DISEASES *of the* CHEST

VOLUME XV. MARCH, 1949 NUMBER 3

A Comparative Study of Sulfadiazine, Penicillin, and Penicillin Combined with Sulfadiazine in the Treatment of Lobar Pneumonia*

ITALO F. VOLINI, M.D., F.C.C.P., JAMES R. HUGHES, M.D. and J. R. PEFFER, M.D.**
Chicago, Illinois

The efficiency of the therapeutic agents in the treatment of pneumococcic pneumonias has been definitely established at this time. However, the common current use of combinations of these drugs with the hope of enhancing their activity prevails. Recently reported mortalities include those of Anderson and Ferguson 12.7 per cent with sulfathiazole, and 11.1 per cent with parenteral penicillin,[1] Collins, Sellers and Kast 6.7 per cent with combined penicillin and sulfadiazine[2] and our experience in previous surveys of 9.6 per cent with sulfadiazine, 4 per cent with sulfapyridine and 6.3 per cent with oral penicillin.[3-5] The variation in these results is certainly small enough, considering statistical errors, to sanction the use of any method indicated. The ease of administration, cost of medication and complicating toxicities must be considered in choosing the most satisfactory mode of arresting pneumococcic infections. The hazard of sensitivity to sulfonamides, the inconvenience of parenteral administration of penicillin and the possibilities of antagonistic activity in combining both medicaments justifies more specific information in selecting the choice of therapy.

Following a recent analysis of a group of patients treated with oral penicillin for pneumococcic pneumonia at Cook County Hospital, Chicago, Illinois,[5,6] a comparative study was undertaken to

*Aided by a grant from the Commercial Solvents Corporation, Terre Haute, Indiana. Presented at the 14th Annual Meeting, American College of Chest Physicians, Chicago, June 20, 1948.

**From the Hektoen Institute for Medical Research of the Cook County Hospital and the Department of Medicine of the Cook County Hospital and Loyola University School of Medicine.

Copyright, 1949, by the American College of Chest Physicians

establish the efficiency of oral and parenteral penicillin as contrasted to sulfadiazine and sulfadiazine combined with intramuscular penicillin. Two hundred and thirty nine patients were included in this study. This total number was subdivided relative to type of therapy as indicated in Table I. Group I included ninety cases treated with sulfadiazine, Group II, 54 cases treated with intramuscular crystalline penicillin, Group III, forty eight cases with oral penicillin and Group IV, 47 cases treated with combined penicillin and sulfadiazine.

Method:

Since the various medical wards at Cook County Hospital receive new admissions in regular rotation regardless of the type of case or severity of illness, it was possible to obtain a satisfactory therapeutic grouping of patients by dividing the wards into segments and arranging for a uniform type of treatment in each segment. In most cases blood culture and sputum examination were obtained. The sputum type was determined by the Neufeld reaction and when this failed, the sputum was cultured on blood agar plates and retyped if pneumococci were found. Blood cultures were incubated 48 to 72 hours and subcultured. In twenty nine cases where the sputums were negative, pneumococci were obtained in this way. Blood was drawn for a sulfadiazine or a penicillin level 48 hours after the initial medication was administered. Chest x-rays were obtained when necessary to confirm the diagnosis.

Dosage and Method of Administration:

Four grams of sulfadiazine were administered as an original dose followed by one gram every four hours around the clock. This was accompanied in most instances by an equal quantity of sodium bicarbonate. Fluids were administered in an amount to insure a daily urinary output of 1500 cc. or more. Daily urinalyses and additional blood counts were obtained during the period of drug therapy. This procedure was continued until all of the patients included in this group were afebrile for 48 to 72 hours.

TABLE I

	Type of Therapy	Number of Cases
Group I	Sulfadiazine	90
Group II	I. M. Penicillin	54
Group III	Oral Penicillin	48
Group IV	I. M. Penicillin with Sulfadiazine	239
TOTAL		239

Intramuscular penicillin was given in the crystalline form in 20,000 unit quantity. The first dose was 40,000 units. This schedule was maintained in all unless evidences of poor response became apparent whereupon the three hour dose was increased to 30,000 units. Supportive measures were used as indicated. All medications were given until the patients were afebrile for 48 to 72 hours.

The oral penicillin used was pure crystalline potassium penicillin assaying slightly over 1500 units per milligram and containing

TABLE II

Typed Pneumococcic Pneumonias

Types	Sulfadiazine			I. M. Penicillin			Oral Penicillin		
	Cases	Bact.	Died	Cases	Bact.	Died	Cases	Bact.	Died
1	7	1	1	5	1		4	3	
2	11	5	3	6	3		9	4	1
3	2			2			1		
4	3			1	1		2	1	
5	4	2	1	2	1		1		
6	2			2			2		
7	4	2	2	2			1		
8				2	1		1	1	
10	3			1			2		
11	1								
12	3			2					
15	1								
16							2		
17	1	1							
32	1								
Pneumococcus failed to type	2	1					1	1	1
TOTAL	45	12	7	25	7		26	10	2
Hemolytic Streptococcus	1		1						
Staphylococcus Aureus	1								
Hemolytic Staphylococcus				1					
Friedlander's Bacillus							1		
Unidentified Bacterial Etiology	43			28		1	21		1
TOTALS	90		8	54		1	48		3

over ninety five per cent penicillin G. Each tablet contained 100,000 units. One hundred thousand units was administered every three hours continuously at 3, 6, 9, and 12 o'clock during the twenty four hours, awakening the patient through the night hours as indicated. A primary dose of 200,000 units was given shortly upon admission to the hospital following the diagnosis of pneumonia. No particular effort was made to separate medication from the ingestion of food as the schedule outlined at the Cook County Hospital permitted both to be given at the same time only at the noon day meal. This method of dosage and drug administration has been reported by us as producing plasma penicillin levels of 0.06 units per cc. or higher during most of the three hour interval between doses. As has been previously indicated,[6] this concentration was found in vitro studies to sterilize cultures of the great majority of strains of the pneumococcus, Group A hemolytic streptococcus, gonococcus and most of the strains of streptococcuc viridans.

Combined intramuscular and sulfadiazine was given in the same dosage as indicated in the above individual groups. Here too, supportive treatment was given when indicated.

Results

Patients in the four therapeutic groups were admitted to the medical wards in the same pneumonia season 1945-1946. Although variations in the symptomatic and supportive measures were adapted to the individual patient, no attempt was made to reserve any of the specific therapy for certain chosen patients. The severity of the pneumonias used in this study is indicated by the incidence of the most virulent pneumococcic organisms, the frequency of multilobar involvement, the presence of bacteremia, associated diseases, the duration of the disease prior to therapy and the age of the patients so infected.

TABLE III

Comparison of Groups and Severity of Illness

	GROUP I *Per cent*	GROUP II *Per cent*	GROUP III *Per cent*	GROUP IV *Per cent*
Incidence of types 1, 2, 3, 7 and 8	53.3	68	61.5	
Bacteremia	26.7	28	38.5	
Duration of disease prior to treatment	4.27	3.89	3.78	3.56
Multilobar involvement	20.0	23.5	29.2	27.3
Age over 50	35.6	22.2	35.4	31.9

Forty five of the 90 cases in the sulfadiazine treated patients (Group I) proved to be of pneumococcic origin (Table II) while 24 (53.3 per cent) of these (Table III) were classified to be of Types I, II, III, VII, or VIII. Group II included 68 per cent of these more serious invaders while Group III showed an incidence of 61.5 per cent. The Bacteremic incidence is indicated as 26.7 per cent, 28 per cent, and 38.5 per cent in the first three respective groups suggesting a more seriously ill class of patients who received oral penicillin. Multilobar involvement was highest in this group also (Table III) being 29.2 per cent as compared to 20.0 per cent, 23.5 per cent, and 27.3 per cent in Groups I, II, and IV, respectively. The duration of treatment prior to therapy was quite constant throughout being somewhat delayed, however, in the sulfadiazine group. These patients also showed the highest incidence of age over 50 (35.6 per cent); the lowest being 22.2 per cent in those cases receiving intramuscular penicillin. Sputum culture, typing and blood culture studies were not available in the pneumonias classified in Group IV. However, the duration of the disease prior to treatment incidence of multilobar involvement and percentage of cases over 50 years of age suggest that these patients were somewhat less severely ill than those treated with sulfadiazine alone or those receiving oral penicillin in Group III. Further evidence indicating this is apparent from the very low number of cases, 15 per cent (Table V) in Group IV having associated

TABLE IV

Mortality According to Age Groups

Age	GROUP I Sulfadiazine			GROUP II I. M. Penicillin		
	Cases	Died	Per cent	Cases	Died	Per cent
Under 50 years	55	7	12.7	41	1	2.4
Over 50 years	32	1	3.1	12	0	0.0
Age unknown	3	0	0.0	1	0	0.0
TOTALS	90	8	8.9	54	1	1.9

TABLE IV (Continued)

Age	GROUP III Oral Penicillin			GROUP IV Penicillin and Sulfadiazine		
	Cases	Died	Per cent	Cases	Died	Per cent
Under 50 years	31	1	3.2	32	3	9.4
Over 50 years	17	2	11.8	15	2	13.3
Age unknown	0	0	0.0	0	0	0.0
TOTALS	48	3	6.25	47	5	10.6

disease. It seems most probable, therefore, that the highest incidence of severe illness was in Group III, those patients receiving oral penicillin. The remaining groups showed approximately equal complicating factors.

All of these cases included in this study are probably not repre-

TABLE V

Associated Diseases

Group I — Sulfadiazine: 26 cases or 29 per cent	
Chronic alcoholism	11
Cirrhosis of liver	1
Latent lues	3
Bronchial asthma	1
Low grade prostatitis and cystitis	1
Severe pyelonephritis	1
Rheumatic heart disease, compensated	1
Hypertensive heart disease, compensated	1
Diabetes mellitus, mild	1
Avitaminosis	2
Arteriosclerotic heart disease	1
Pulmonary tuberculosis	1
Cellulitis and lymphangitis thigh from burn	1
Group II — I. M. Penicillin: 13 cases or 24 per cent	
Chronic alcoholism	8
Cirrhosis of liver	1
Latent lues	1
Epilepsy	1
Rheumatic heart disease, compensated	1
Congenital deformity of thorax with scoliosis	1
Group III — Oral Penicillin: 17 cases or 35 per cent	
Chronic alcoholism	6
Cirrhosis	2
Pulmonary tuberculosis	3
Hypertensive heart disease	1
Bronchial asthma	1
Bronchiectasis with pulmonary arthropathy and arteriosclerosis	1
Arteriosclerotic heart disease with auricular fibrillation, decompensated	1
Rheumatic heart disease, compensated	1
Acute pyelitis	1
Group IV — Penicillin combined with Sulfadiazine: 7 cases or 15 per cent	
Chronic alcoholism	3
Arteriosclerotic heart disease, compensated	2
Arteriosclerotic hypertensive heart disease, compensated	1
CNS lues	1

sentative of the average pneumonia encountered in routine practice because of the frequency of prolonged exposure noted prior to hospitalization and a greater incidence of malnutrition encountered in patients entering a large charitable institution. The pneumonias under consideration here, therefore, are considered to be representative of the more severe cases of pneumonic infection than those seen in every day medical practice.

Blood concentrations of the therapeutic agents used were determined in all patients and these have been reported as adequate for the in vitro sensitivities of pneumococci recovered on culture. It is not the purpose of this paper to indicate clinical febrile response or efficiency of individual type of therapy as this has been reported by us in numerous previous publications. These results are considered on a comparative basis only, the relative efficiency of treatments.

Adequate therapeutic response was measured by the effect of therapy on fever, the mortality rate, the duration of treatment and the incidence of complications in the various therapeutic groups. A comparison of clinical febrile control is indicated in

TABLE VI
Duration of Treatment

Days	GROUP I Sulfadiazine	GROUP II I. M. Penicillin	GROUP III Oral Penicillin	GROUP IV Penicillin with Sulfadiazine
Average duration treatment	6.9	5.5	5.8	7.7
Maximum duration treatment	20.0	18.0	20.0	18.0
Minimum duration treatment	3.0	3.0	3.0	3.0

TABLE VII
Total Dosage

	GROUP I Sulfadiazine	GROUP II I. M. Penicillin	GROUP III Oral Penicillin	GROUP IV Penicillin with Sulfa Diazine	GROUP IV Penicillin with Sulfa Penicillin
Average total dose	39.5 g.	870,000 u.	4,410,000 u.	45.1 g.	1,212,340 u.
Maximum total dose	107.0 g.	2,720,000 u.	14,400,000 u.	94.0 g.	2,720,000 u.
Minimum total dose	15.0 g.	400,000 u.	2,100,000 u.	23.0 g.	420,000 u.

Ratio of quantity oral penicillin to parenteral penicillin — 5.07/1

Table VIII. The most rapid decline of fever, within 24 hours or less, was noted in the patients receiving oral penicillin (Group III), 37.5 per cent. During a three day period of evaluation, complete control of fever showed a higher incidence in the patients receiving intramuscular penicillin every three hours (68.5 per cent). Oral penicillin was next in effectiveness (62.4 per cent), sulfadiazine third and combined therapy least with only 40.4 per cent response in this period of time. The duration of fever for more than 72 hours was likewise most frequently noted in Group IV (sulfadiazine plus penicillin) and least frequently noted in those receiving intramuscular penicillin and oral penicillin respectively. It is apparent from these figures that combined therapy proved to be the least effective on the febrile courses of these patients with pneumococcic pneumonias.

The mortality rates in the various groups is indicated in Tables VIII and IX. Here again combined therapy was proven to be the least effective as five deaths were recorded in the total 47 patients (10.6 per cent). Only two of these patients were over 50

TABLE VIII

Effect of Therapy on Temperature

Duration of fever following onset of treatment	GROUP I Sulfa *Per cent*	GROUP II I. M. Penic. *Per cent*	GROUP III Oral Penic. *Per cent*	GROUP IV Combined *Per cent*
24 hours or less	25.3	33.3	37.5	6.4
24 to 48 hours	18.4	20.4	20.8	10.6
48 to 72 hours	13.8	14.8	4.1	23.4
Total becoming afebrile within 72 hours	57.5	68.5	62.4	40.4
Duration of fever more than 72 hours following onset of therapy	33.6	29.6	31.3	48.9
Expired	8.9	1.9	6.25	10.6

TABLE IX

Mortality

GROUP I: Sulfadiazine			GROUP II: I. M. Penicillin		
Cases	Died	Per cent	Cases	Died	Per cent
90	8	8.9	54	1	1.9

TABLE IX (Continued)

GROUP III: Oral Penicillin			GROUP IV: Combined		
Cases	Died	Per cent	Cases	Died	Per cent
48	3	6.25	47	5	10.6

years of age, one with arteriosclerotic heart disease and the other developed a marked pleural effusion. No other associated disease were recorded in this group. The lowest mortality was 1.9 per cent in Group II receiving intramuscular penicillin every three hours. This represented the only death in 54 patients receiving this type of therapy. It occurred in a patient 54 years of age with a delay in treatment of 5 days following the onset of the disease. Three deaths were noted in the patients receiving oral penicillin with a mortality rate of 6.25 per cent. One of these was 68 years of age and another 55 years old. All three were handicapped with associated disease including bronchiectasis, generalized arteriosclerosis and severe emphysema in the first and delirium tremens with bacteremia in the second. The other had manifest evidence of malnutrition with a positive blood culture. The second largest mortality occurred in those receiving sulfadiazine (Group I). There were 8 deaths in 90 patients here, an incidence of 8.9 per cent. Only one of these patients was over 50 years of age and associated disease was present in only five.

The occurrence of complications following the onset of treatment was greatest in Group IV as indicated in Table X. Eight

TABLE X
Complications

	Cases	Percentage	Died
Group I — Sulfadiazine: 90 cases			
Empyema	2	2.2	2
Pleural Effusion	2	2.2	0
Toxic Hepatitis	1	1.1	0
Prerenal Azotemia	1	1.1	0
Group II — I. M. Penicillin: 54 cases			
Empyema	2	3.7	1
Lung Abscess	1	1.9	1
Toxic Hepatitis	4	7.4	0
Group III — Oral Penicillin: 48 cases			
Empyema	1	2.17	1
Pleural Effusion	3	6.25	0
Pneumococcic Meningitis	1	2.1	1
Toxic Hepatitis	1	2.1	0
Group IV — Penicillin combined with Sulfadiazine: 47 cases			
Empyema	1	2.1	1
Pleural Effusion	3	6.4	0
Toxic Hepatitis	2	4.3	0
Toxic Psychosis	1	2.1	0
Prerenal Azotemia	1	2.1	0
Prerenal Azotemia	1	1.1	0

cases (17 per cent) included empyema, pleural effusion, toxic hepatitis, toxic psychosis and pre-renal azotemia. This group of patients, as was previously indicated, included the least number of patients with associated disease. Twelve and six tenths per cent of those receiving oral penicillin developed complications. In these, two deaths were recorded; one with empyema, and the other with pneumococcic meningitis. Each, however, was over 50 years of age, and was handicapped originally by bronchiectasis and chronic alcoholism with delirium tremens. Thirteen per cent of the patients in Group II developed complications and 6.6 per cent in Group I.

The duration of therapy is indicated in Table VI. This was greatest in Group IV (combined medication), averaging 7.7 days. Treatment in patients receiving intramuscular penicillin (Group IV) averaged 5.5 days and 5.8 and 6.9 days respectively with oral penicillin and sulfadiazine.

The average total dosage of chemo-therapeutic or antibiotic agents is indicated in Table VII. The quantity of intramuscular penicillin given with sulfadiazine is very close to that given alone intramuscularly. The total oral penicillin was approximately five times that of the total intramuscular penicillin. The sulfadiazine administered in Group I was less in total quantity than that combined with penicillin.

Discussion

The multiplicity of studies on various modes of the use of penicillin have demonstrated effectiveness by each method. This is illustrated first by the oral route, secondly, in a study by us, by single daily massive intramuscular penicillin in peanut oil and beeswax, and thirdly, by the use of intramuscular aqueous penicillin.

Concentrations of 0.03 units of penicillin per cubic centimeter of blood controls the commoner etiological organisms producing pneumonia. This concentration is easily and readily obtained by the methods of administration which have been indicated and have been confirmed by numerous published results, and by investigators from the Hektoen Institute of Cook County Hospital. It is, therefore, reasonable to assume that a single effective agent which experimentally and clinically has demonstrated superiority over the sulfonamides, should be used alone.

There is no infection occurring in the pulmonary system in which the sulfonamides have been proven to be even the equal of penicillin. It seems, therefore, unreasonable that, unless there is a definite indication, such as the inability of the patient to accept penicillin because of hypersensitivity to this antibiotic, that

the sulfonamide should be added or substituted in the treatment. It is further unreasonable to assume that where organisms demonstrate a very high degree of penicillin resistance that they should a-priori be sulfonamide susceptible. The indications for the combined use of these two drugs at the present time would seem to be the attitude of the therapist to bring into action all of the therapeutic armamentarium which he possesses. We believe we have demonstrated this to be in error, therapeutically speaking. In analyzing the total dose of therapeutic agents used, the quantity of each, chemo or antibiotic when combined was equal to or slightly in excess of the amounts given alone. If the above reasoning were in order, some evidence should have been noted to encourage the use of this type of therapy. All aspects of clinical response which might indicate a beneficial response to combined treatment was lacking. The mortality rate was higher, the febrile course was prolonged, the incidence of complications was greater, and the duration of treatment was lengthened. All of these unfavorable results occurred in a group of patients who after analyzing them proved to be clinically less ill than those considered in the other comparative groups. These patients were subjected also to the unpredictable toxic reactions associated with the administration of the chemotherapeutic agents.

In a very few instances which we have experienced of penicillin allergy, control of this complication by anti-histamine drugs is relatively simple because of the low blood level assays of penicillin required to overcome the infection in patients invaded by the pneumococci.

Sulfonamides potentially have a much greater toxicity than penicillin. Therefore, their use must be supervised with greater caution. Fluid intake, output and urinary studies, both the reaction and the sediments must be observed frequently and carefully. Despite all of these precautions, serious complications from sulfonamide medication may occur.

Multi-medication having to be watched by the physician means additional disturbance and iritation to the patient. The increasing incidence, demonstrated by post mortem examination, not alone the lower nephron block, but interstitial sulfonamide nephritis with generalized distribution of similar allergic lesions means a much greater hazard to the patietn.

Klein and Kalter[7] have indicated that the additional use of the sulfonamides in the body produces no increase in the penicillin titre unless both agents are present in definitely inhibitory concentration levels. The administration of a therapeutic agent on this basis seems impractical, because, as was previously indicated, the quantity of each medication as combined was equal to or

slightly greater than that used alone. Furthermore, there is no apparent need for a higher titre as the currently popular dosage has been proven more than adequate for bacteriostsis to pneumococci. Hobby and Dawson[8] concluded that the vastly more complex nature of the conditions which may be encountered in vivo studies over in vitro assays indicate that it is impossible to determine in advance whether or not sulfadiazine will enhance the bacteriostatic action of penicillin in human infection. The clinical evidences presented herein indicate the possibility of an antagonistic action in combined therapy rather than a synergistic activity.

SUMMARY AND CONCLUSIONS

1) This statistical comparison readily demonstrates that penicillin is a much more superior drug than sulfadiazine in the treatment of pneumococcic pneumonia.

2) Sulfadiazine is an inferior therapeutic agent for the treatment of pneumonia as compared to the antibiotic, penicillin.

3) The evidence adduced in these series of investigations, demonstrate that in the group in which there was addition of sulfadiazine to the antibiotic therapy, there was a delayed clinical response, a greater incidence of complications, and a higher mortality.

4) The clinical use of sulfadiazine with penicillin indicates a possible antagonistic action in vivo rather than a synergistic effect.

5) There is little justification for the combined administration of the sulfonamides and penicillin in the treatment of pneumonia. Penicillin alone will accomplish the therapeutically desired goal if this is attainable.

6) There are very, very few pneumonia patients who cannot be treated with penicillin. They may require sulfonamide therapy.

RESUMEN Y CONCLUSIONES

1) Esta comparación estadística demuestra fácilmente que la penicilina es una droga muy superior a la sulfadiazina en el tratamiento de la neumonía neumocóccica.

2) La sulfadiazina, comparada con el antibiótico penicilina, es un agente terapéutico inferior en el tratamiento de la neumonía.

3) Las pruebas presentadas en estas series de investigaciones demuestran que en el grupo en el que se añadió la sulfadiazina a la terapia con el antibiótico la respuesta clínica fue demorada y hubo una mayor frecuencia de complicaciones y una mortalidad más elevada.

4) El uso clínico de la sulfadiazina con la penicilina indica una posible acción opuesta *in vivo* en vez de un efecto sinérgico.

5) No se justifica la administración de las sulfonamidas y la penicilina combinadas en el tratamiento de la neumonía. La penicilina sola realiza el propósito terapéutico deseable si es posible alcanzarlo.

6) Hay muy pocos pacientes con neumonía que no pueden ser tratados con penicilina. Estos casos pueden requerir la sulfonamidoterapia.

REFERENCES

1 Hoffman, Wm. and Volini, I. F.: "Studies in the Oral Administration of Penicillin, I. Assays of Various Preparations and the Determination of the Effective Therapeutic Dose," *Am. J. M. Sc.*, 213:513-519, (May) 1947.

2 Collen, M. F., Sellers, A. L. and Kast, E. C.: "Combined Penicillin and Sulfadiazine Therapy in Pneumococcic Pneumonia," *Am. J. M. Sc.*, 11:299-306, (March) 1946.

3 Volini, I. F., Engbring, G., Peffer, J. and Schorsch, H.: "The Treatment of Pneumonia with Sulfadiazine," *M. Clin. N. Amer.*, 28:267-277, (Jan.) 1944.

4 Volini, I. F. and Levitt, R. O.: "The Sulfapyridine Treatment of Pneumococcic Pneumonia," *Illinois M. J.*, 78:305-314, (Oct.) 1940.

5 Volini, I. F., Hoffman, Wm., Hughes, J. R. and Peffer, J. R.: "Oral Penicillin in the Treatment of Pneumococcic Pneumonia." Accepted by Illinois M. J.

6 Hoffman, Wm. and Volini, I. F.: "Studies in the Oral Administration of Penicillin, II. Results of Treatment of Lobar Pneumonia and Other Acute Infections with Several Oral Preparations," *Am. J. M. Sc.*, 213: 520-53, (May) 1947.

7 Klein, M. and Kalter, S. S.: "The Combined Action of Penicillin and the Sulfonamides in Vitro; The Nature of the Reaction," *J. Bact.*, 51: 95-105, (Jan.) 1946.

8 Hobby, G. L. and Dawson, M. H.: "Effect of Sulfonamide on the Action of Penicillin," *J. Bact.*, 51:447-456, (April) 1946.

9 Romansky, M. J. and Rittman, G. E.: "Penicillin Blood Levels for 24 Hours Following Single Intramuscular Injection of Calcium Penicillin in Beeswax and Peanut Oil," *New England J. Med.*, 233:577-582, 1945.

Discussion

HARRY F. DOWLING, M.D.
Washington, D. C.

It seems to me there are two distinct parts of this subject. The first is, is penicillin better than the sulfonamides, and the second, is the combination better or worse than penicillin alone. We have treated 1250 patients with sulfonamides, all of whom had pneumococcic pneumonia, and more than 800 with penicillin. Approximately 9 per cent of the patients died when given sulfonamides,

and 4.5 per cent died when they were given penicillin; that is, half as many of those receiving penicillin died as compared with those receiving sulfonamides.

It does not matter, apparently, what kind of penicillin one uses—at least we have not been able to demonstrate any difference between the different types, providing penicillin is used in adequate doses.

Regarding the second question, as to whether the combination is better or worse than the use of penicillin alone; we cannot find any difference. Some time ago we ran a parallel series in which we used sulfadiazine on 90 patients and sulfadiazine plus penicillin on another 90 patients, and we had a case fatality rate of about one-half as great when we used penicillin plus sulfadiazine. In other words, again about 9 per cent for sulfadiazine compared with 4.5 per cent with the combination. I am at a loss to account for Dr. Volini's results with a seemingly greater case fatality rate in those patients who had the combination, unless it was due to the small number of patients included in his series. Because, as we know, in pneumococcic pneumonia patients who have delirium tremens or cardiac failure, or who are quite old, or who have some other complication, may die and throw the case fatality rate away over if only a small number of patients are used in the series. Dr. Volini was not able to use all his patients, because he wanted to take the entire group from one year, and yet I feel that he should continue his work into other years so that we would have a definite answer to this problem. Personally, I cannot see that the sulfonamides will cause an increase in the case fatality rate, and I feel, along with him, that we should use penicillin alone and not penicillin plus sulfonamides.

One other thing might be said. There are certain organisms infrequently the cause of pneumonia such as Klebsiella pneumoniae (or Friedlander's bacillus) and Hemophilus influenzae, which will not respond to penicillin and which will respond to sulfadiazine. In those cases the patient may be given sulfadiazine or, better still, sulfadiazine plus streptomycin. The practical compromise we have evolved is to collect a specimen of sputum from every patient as soon as the diagnosis, or tentative diagnosis, of pneumococcic pneumonia is made and put it in the refrigerator. We have found that typing after three or four days is just as good on those specimens as on fresh specimens. Then if the patient does not do well in 48 hours, sulfadiazine may be added tentatively, typing of the sputum may be done, and cultures made. Then you can see whether you have a type of pneumonia which needs other therapy, namely, sulfadiazine plus streptomycin. I hope Dr. Volini will continue his work.

Closing Remarks

Italo F. Volini, M.D., F.C.C.P.: I wish to thank Dr. Dowling for his remarks and most assuredly we shall continue this line of investigation. I would like to call to mind the time when we were using rabbit serum. When the sulfonamides were introduced, I think we first called attention to the fact that the combination therapy of immune rabbit serum and the sulfonamides produced a greater mortality than where sulfonamides were used alone. That, in fact, prompted this study. It was a small group of patients in which I demonstrated these results and it was not until the Pneumonia Control Commission of Pennsylvania evaluated their statistics in a large group of cases, that we were able to find out conclusively that such a combination was not as satisfactory as the use of sulfonamides alone.

The re-administration of sulfonamide therapy after an intermission is probably a very important factor in the sensitization of patients to sulfonamides. Very frequently we have been unable to obtain a history of previous sulfonamide administration until the patient manifests serious toxic signs. The indications for sulfonamide therapy today I believe are greatly restricted and I think are becoming more and more so, due to the availability of penicillin and as Dr. Dowling mentioned, streptomycin, which will take care of many of these resistant organisms that do not respond to penicillin, and against which streptomycin is a better agent than is sulfonamide. Sulfonamide medication today can be pushed down to very few indications, in my opinion. Since I have seen so many of these individuals demonstrating the serious toxic manifestations of lower nephron block and of interstitial nephritis at the postmortem table—those general allergic findings which are comparable to the investigations of Rich at Johns Hopkins in his sensitization studies—we have felt that the sulfonamides can be restricted to use in the meningitides, due particularly to the meningococcus, pneumococcus and other pyogenic cocci. However, many of these must receive penicillin by parenteral injections. In the pre- and postoperative care of patients selected for surgery of the bowel, the unabsorbable types of sulfonamide are particularly useful. In cases of bacillus dysentery infection, in some cases of lymphogranuloma venereum, they are useful. Thus there are relatively few indications today for the use of sulfonamides, due to the introduction of the antibiotics, penicillin and streptomycin.

Chronic Nontuberculous Pulmonary Infections and Their Sequelae*

ALVIS E. GREER, M.D., F.A.C.P., F.C.C.P.
Houston, Texas

FORWORD

The role of chronic nontuberculous infections as a cause of human misery and disability has not been adequately appreciated. The initial, causative factor, primarily seemingly insignificant and justifying scant consideration, may eventually pass through a series of conditions, leading in the end to invalidism and even death. It is my purpose in this paper briefly to sketch the course of chronic nontuberculous infections from the beginning through their progressive stages to their end results, such as, pulmonary fibrosis, cavitation, and bronchiectasis.

It is impossible to deal separately and fully with each of the etiologic agents involved in these infections, but reference will be made to the role of chronic lobar and chronic bronchopneumonia, aspiration pneumonitis, atelectasis, pneumonoconiosis, bronchial and bronchiolar stenosis, metastatic lung infections, the mycoses and syphilis, as well as the milder, but quite important, chronic infections of the nasaopharynx and bronchi. It is necessary to stress the role in the initial development of these chronic infections of such conditions as acute nasosinusitis, subacute bronchitis, and the acute pneumonias. A closer cooperative understanding between the nose and throat specialist and the general practitioner would be helpful in diagnosing and eradicating suppurative conditions of the nasal sinuses. These infections are often given palliative treatment, only to recur each winter, until a chronic bronchitis and eventually a chronic pneumonitis and bronchiectasis may develop. The dreadful end results could be, in many cases, obviated in the beginning by prompt treatment, and by carefully following the patients through to a cure. Patients following attacks of acute pneumonia should be regularly checked for the presence of residual foci of infection in their lungs; small atelectatic areas, single or multiple, small bronchopneumonic areas, and slight abscesses, may be found to reward us for our diligence.

---

*Presented at the Arizona Chapter, American College of Chest Physicians, Phoenix, Arizona, May 1946.

Bacteriology

The bacteriology of chronic nontuberculous pulmonary infections, is well worth considering. Petroff and Schwartz[1] in an excellent study have stressed that the bacteriology of chronic nontuberculous pulmonary infections has not kept apace with other methods for diagnosis. They discuss the bacteriology of these pulmonary infections by studying three types, namely, lung abscess and gangrene, bronchiectasis, and pulmonary infections which simulate pulmonary tuberculosis or at times may occur in symbiosis with tuberculosis. They state that abscess of the lung is not due to a specific micro-organism but is the result of various types, differing as to the kind of abscess found; anaerobic bacteria, such as vibrios, anaerobic streptococci, and fusospirochetal organisms especially being the main causative factors in producing putrid lung abscess and gangrene; aerobic, nonputrid, lung abscess having the pyogenic bacteria, diplococcus pneumoniae, Hemophilus influenzae, Neisseria catarrhalis, diphtheroids, streptococci and especially staphylococci predominating; mycotic suppurative processes, frequently simulating tuberculosis, may be caused by actinomyces, moniliae, aspergilli, penicillia, and coccidiodes, and to a lesser extent by many other fungi, especially of the fungi imperfecti group. It is understood that tubercle bacilli are always absent in the sputum of these patients.

Etiologic Diseases

Although some of these patients may present an acute, and at times a stormy onset, the process develops more gradually in a large percentage of them. A simple bronchitis, following an acute nasopharyngeal infection, for instance, may lead to an extension of the infection into the wall of the bronchi with areas of pneumonitis resulting. The general health of the patient may be practically unimpaired, although there may be a tendency during exacerbations to increased cough and some fever. The majority are in full adult life. The period of increased symptoms is usually during the colder, winter months. Cough and expectoration may be the only symptoms, although fever, pleurisy, and even hemoptysis may occur. The lesions are ordinarily in the lower lobes, especially the left. It is interesting to recall that with the recurring exacerbations the physical findings have a marked tendency to recur in their original location. The similarity of the clinical findings to early pulmonary tuberculosis is striking, but the distinction between the two entities is aided by the basal location of the physical and roentgenologic findings in the nontuberculous individual, in contradistinction to the upper lobar findings in the

tuberculous patient. It is possible the pathology in these cases may be a localized bronchitis with lobar or lobular distribution involving the submucous and peribronchial tissues. This condition may clear up after an attack and recur at a later date, or persist in a latent subacute form. In this latter case, the acute recurrences affect the original site and are probably due to a localized lesion. This may lead into chronic interstitial pneumonia or bronchiectasis. It is my opinion that these recurring episodes are due, not to new acute infections, but to recrudescences of the same infection which has been lying dormant in the lungs during the interium between flare-ups.

It has been indicated heretofore that conditions other than described in the proceeding paragraph may be operative in producing chronic nontuberculous pulmonary infections. Some consideration of these conditions will be mentioned.

Pulmonary Abscess and Gangrene

Pulmonary abscess and gangrene[2,3] may follow aspiration of foreign material after surgical operations, pneumonia, wounds to the lungs, the presence of carcinoma of the bronchus, lung or esophagus, and rarer infections such as mycoses, cysts or the extension of suppuration from beneath the diaphragm, liver or perirenal tissues. They are not specific diseases because they are due to a wide array of bacteria. Bucher[4] in a study of the pus obtained bronchoscopically in 118 cases of pulmonary abscess found 18 different organisms, with the streptococcus (hemolyticus, viridans, nonhemolyticus), micrococcus catarrhalis, pneumococcus, bacillus influenzae, staphylococcus albus and aureus, diphtheroid bacilli, spirochetes, fusiform bacilli and the micrococcus tetragenes predominating. Rona[5] in 1905 first recognized fusiform bacilli in pulmonary gangrene. Oliver and Wherry[6] in 1921 first described the bacterium melaninogenicum, and since that time this strictly anaerobic, non-motile, polymorphic and gram-negative organism in symbiosis with other bacteria has been shown to produce extensive tissue necrosis in the lung. Unless this acute process heals, a chronic abscess associated with bronchiectasis may ensue.

Chronic Lobar and Bronchopneumonia

Especially after influenza, measles and whooping cough, an acute broncho-pneumonia may be followed by a chronic progressive pneumonitis, or the development of atelectasis and bronchiectasis. In some cases of lobar pneumonia resolution of the lung tissue may not occur promptly, and rarely abscesses may be followed by cavitation, or another group may develop a chronic course through

many months or years. We have seen a case of acute Friedlander's bacillus pneumonia assume a chronic form which lasted for years, and closely resemble the clinical picture of chronic tuberculosis.

Aspiration Pneumonitis

The aspiration of foreign bodies, especially those of an organic nature, may give rise to bronchial and peribronchial inflammation and suppuration, usually in the hilar or midportions of the lungs. It is clear that these unfortunate conditions may be obviated only by making roentgenograms at once when there is a likelihood of a child aspirating any foreign material.

Atelectasis

Atelectatic areas, occurring in infants at birth, or from massive collapse following operations in any age group, may become infected; at first the bronchial and bronchiolar mucous membranes are involved, later the infection may spread to the peribronchial tissues. A focus for subsequent exacerbations of infection may follow, and be erroneously termed "bronchitis," or, if the recurring attacks of acute pneumonitis be more severe, they may be diagnosed "pneumonia." As time passes on, a chronic recurring, localized pneumonitis develops and may last for many years.

Bronchial and Bronchiolar Stenosis

It is well recognized that the occlusion of the bronchi or bronchioli may precipitate the development of atelectatic areas distal to the obstruction, and that a chronic pneumonitis may develop with either bronchiectasis or pulmonary abscess occurring, singly or together. An inflammatory condition of a bronchus, a benign or malignant bronchiogenic tumor may be the etiologic agent.

Metastatic Lung Infections

A chronic, relatively mild pulmonary infection may follow metastatic pulmonary emboli. The clinical picture will vary according to whether the emboli are large, or small and numerous; a serious localized abscess may follow a large embolus, whereas small, multiple emboli may rarely produce a chronic recurring pneumonitis.

Pneumonoconiosis

Workers on sandstone and quartz, or any combination of large amount of silica, frequently suffer from chronic pneumonitis and nodular pulmonary fibrosis often follows.

Syphilis

Many years ago in a study[7] of the incidence of syphilis in the Houston Anti-tuberculosis Clinic, I was impressed with the belief

that pulmonary syphilis is more frequent than is commonly believed to be true. About 1 in 250 cases, previously diagnosed as tuberculosis, was believed to have pulmonary syphilis. The patients were largely drawn from Negro and Mexican admissions. Single or multiple gummas were noted, as well as definite fibrotic streaking and thickening of the bronchial and peribronchial tissues.

Mycoses

Meakins[8] lists four mycotic diseases of the lungs, namely, blastomycosis, actinomycosis, streptothricosis, and aspergillosis. The term blastomycosis is used in a general sense, meaning the various fungi reproducing by blastospores; the so-called "yeast-like" fungi—the cryptococcus, monilia, torula and oidium. Actinomycosis and streptothricosis may be classified under the nocardia, and distinguished by the fact that a case of streptothricosis has no granules in the sputum and actinomycosis has. Aspergillosis is a very chronic disease and runs a mild course. We have previously stressed the insidiousness and latency of mycotic infections of the lungs. The clinical course of these invasions may be quite similar to chronic fibrosing pulmonary tuberculosis. The diagnosis may be difficult, and should never be made from the expectorated sputum alone. In a personal study[9] of 301 patients, fungi were isolated from the expectorated sputum in 45 patients; in 18 patients (6 per cent) we isolated fungi from tracheal washings. We considered the other 27 fungi contaminants and pathogenic; the saprophytic fungi were of the following genera: cryptococcus Kützing, monilia Persoon, sporotrichum Link, acremonium Link, saccharomyces Meyen, and aspergillus Micheli. The saccharomyces, constituting 64 per cent of the fungi classed as contaminants, were consistently saprophytic and parasitic. There were 5 cases of pure mycoses, identified as 1 aspergillus fumigatus, 1 cryptococcus hominis Vuillemin, and 3 sporotrichum Schenki; an incidence of 1 to 60 mycotic to tuberculous patients. Although fungous infections, occurring as single entities, usually run a benign, but protracted course, we believe fungi, when associated with tuberculosis, enhances the activity of the tuberculous process.

Classification

Chronic nontuberculous pulmonary disease may be classified on an anatomical and pathological basis according to the following table;[10]

I. Bronchial Tube Disease
   A. Reactive injury
      1. Mucous membrane—reaction "catarrhal bronchitis"
      2. Bronchial wall—reaction "mural bronchitis"

B. Traumatic injury
   1. Bronchial obstruction
   2. Bronchial dilatation

II. Air Cell Disease
   A. Reactive injury
      1. Pneumonia
         a. Inflammatory
         b. Organized
   B. Traumatic injury
      1. Pulmonary collapse (atelectasis)
      2. Pulmonary over-expansion
         a. Diffuse (emphysema)
         b. Localized (pulmonectasis)

There is a type of bronchitis, which Andrus[11,12,13] terms idiopathic, occurring in a large group of people, characterized by chronic cough and expectoration, which does not result in a chronic pneumonia, fibrosis, bronchiectasis, etc. This is the so-called "catarrhal bronchitis." There is a similar group showing in the radiographs some thickening of the bronchial tree, due to reactive changes in the bronchial walls. This is the "mural bronchitis" of the previously listed table, and the bronchial wall reaction is a postpneumonic type of injury. The radiographic shadows in mural bronchitis may be due, however to an arteriosclerotic process. It has been shown from Robinson's[14] studies on surgically removed bronchiectatic lobes that the infection probably passes from inside the bronchial wall, rather than from within the lumen of the bronchi, because he found normal mucuous membrane and functioning cilia in the bronchi in such cases. We may, then, have two distinct types; catarrhal bronchitis (x-ray negative), mural bronchitis (vascular, infectious) (x-ray positive). Traumatic injury to the bronchi may be due to either, or both, obstruction or dilatation of the tube. The presence of a major area of atelectasis indicates obstruction of one of the larger bronchi; smaller, patchy atelectatic areas the result of a bronchiolar stenosis as may be found in bronchopneumonia.

Chronic disease of the alveolar air cells may be caused by either inflammatory or traumatic injury. There may be a shrinkage or an overexpansion of the pulmonary tissues. Pulmonary shrinkage, caused by contraction of scar tissues, may be extensive or "patchy" in distribution. It should be stressed that postpneumonic lung shrinkage is more likely to be caused by pulmonary collapse than to fibrosis, although fibrosis usually follows atelectatic collapse. The primary underlying factor in the production of chronicity in nontuberculous lung disease is atelectasis. Pulmonary overexpan-

sion is a compensatory mechanism, when the volume of the chest contents is reduced by localized shrinkage, or the capacity of the thoracic cage is increased by outward displacement of the chest walls. The overexpansion may be diffuse or localized. The localized type is due to an infection with a persisting chronic patchy atelectasis, and consists of localized emphysematous air blebs. Andrus calls this latter condition "pulmonectasis," and a chronic infection and overdistension of the pulmonary bases, formerly listed as unresolved pneumonia, chronic basal disease, pneumonitis and bronchiectasis—suspect could fall in this category.

B. *End Results*

It has been suggested by Miller[15] that bronchiectasis is of congenital origin, but the wide concensus of opinion is that a congenital origin is doubtful. In my opinion the secondary factors, bronchial obstruction and atelectasis, with an infection following such a mechanical obstruction, seems more plausible as etiologic factors in a preponderant percentage of cases. It must be added, however, that congenital bronchiectasis may occur, although we are not especially concerned with a discussion of the congenital type in this paper. Ballon and Ballon[16] have classified five types of bronchiectasis, based on iodized oil injections, as follows: grape, clubbing, cylindrical, saccular, and bead formation. The symptomatology may be quite varied, in fact lacking in early cases, and consist only of the subjective and objective signs of the primary causative disease. As time runs on, the clinical picture gradually changes, and new added symptoms come into prominence. Cough and expectoration may be the only distinct symptoms. The cough may be hacking, persistent or severe, dry or productive. The inhalation of substances, such as tobacco smoke or gases, may be very irritating. The sputum[17] contains a large amount of water and albumin, peptones, amino acid, pus and bacteria; it usually has a foul odor, and may exceed 1000-15000 cc. in 24 hours, being expectorated more or less persistently, or more usually, paroxysmally. The sputum, ordinarily but not regularly, separates after expectoration into three or four layers; a pale greenish-yellow layer of air bubbles, mucus and pus; a mid-layer of pus cells, fat rests, Dittrich's plugs, and detritus. The foul odor of the sputum may be distressing to the patient and as previously stated is due to the presence of anaerobic organisms. More advanced cases of bronchiectasis may have fever, sweats and chills. These episodes are due to attacks of recurring pneumonitis and not to retained intrabronchial secretions. It follows, therefore, that fever may continue, even though the bronchial secretions are expectorated. Especially in cases of numerous smaller bronchial or bronchiolar

dilatations it must be assumed that pneumonitis is present when toxic manifestations, fever and sweats, are present. Hemoptysis is frequently noted. Joint pains may also be associated. The physical findings are not typical, although they are usually basal in location, in contradistinction to the findings in tuberculosis, which are more likely to be apical. There may be increased voice conduction (pectoriloquy) or decreased breath sounds, and most always rales. Signs of localized atelectasis or even cavitation may be present. There is usually a moderate, secondary type of anemia and some polymorphonuclear leucocytosis. The organisms in the sputum consist of the great array previously discussed. The diagnosis, although to be strongly inferred from the history, symptoms and physical findings, is not complete without iodized oil injection. The normal primary and secondary divisions of the bronchi do not cast a radiographic shadow, and although a diseased bronchus does cast a shadow, it is very difficult to decide whether the shadow is due to the bronchus itself, or to a peribronchial pathology. Therefore, for exact diagnosis of bronchiectasis, iodized oil injection is essential. Bronchoscopy is of great help in that obstructive new growths in stenotic conditions may be found, the discharging pus may be localized, the iodized oil injection may be more accurately made, and uncontaminated cultures may be obtained. Singer[18] has stated that a diagnostic pneumothorax may reveal a bronchiectatic, atelectatic lobe, hidden in the cardiac shadow. It is my opinion that advanced bronchiectasis is incurable by the ordinary remedial agents, although they may be definitely palliative. The disease is characterized by remissions, and it is difficult to judge the value of rest, climate, postural drainage, vaccine, drug therapy, or local treatment, such as direct intrabronchial application of drugs, bronchial lavage and inhalations.

Considerable pulmonary fibrosis, with chronic pneumonia and abscess formation, may be expected to be found in many, if not most, cases of definite bronchiectasis. It has been shown that an exudate in the alveoli of the lungs may become vascularized and fibroblasts and capillaries, with the formation of connective tissue, ensues. Scar tissue will ultimately distort the bronchi and make emptying impossible. The added presence of pneumonic patches and fibrinous pleuritis, resulting in parenchymal fibrosis and adherent pleura, respectively, further distort the bronchi and the pulmonary tissues and the chest cage. Chronic abscesses may form in the resulting atelectatic areas; these may empty periodically through the bronchus, or, when they are numerous and small, may remain as purulent foci within the lung tissues.

The ultimate fate of these patients depends upon the type and prominence of the bronchiectatic process, and the extent of com-

plicating factors, such as pulmonary fibrosis and recurring pneumonitis, abscesses, the presence of scar tissue, the degree of intrathoracic distortion of the heart and mediastinal contents, and the associated cardiovascular and toxic phenomena. Severe cases may die in a relatively short time from fulminating hemoptyses, acute pneumonia or abscess, or they may survive many years. Eventually the latter cases die from a severe recrudescence of the bronchiectatic and associated conditions, or from the more gradual development of cardiac failure, amyloidosis, or general nutritional failure from chronic toxemia.

SUMMARY

It should be evident from this review that the early treatment and eradication of acute and subacute disease entities within the respiratory system, is positively necessary if we are to expect to obviate their serious sequelae. The best treatment is, therefore, preventive, and little may be expected from medical measures after these chronic infections have become evident. It is the main and primary object of this discussion of chronic nontuberculous infections of the lungs to stress the urgent necessity of diagnosing the earliest etiologic pathologic states, which lead otherwise to an incurable and serious disease, and, do all in our power to promote, if possible, their prompt and thorough eradication.

RESUMEN

Este repaso debe hacer evidente que el tratamiento temprano y la erradicación de las enfermedades agudas y subagudas del sistema respiratorio son absolutamente necesarios si hemos de abrigar esperanzas de evitar sus graves secuelas. El mejor tratamiento es, por consiguiente, profiláctico, y poco se puede esperar de medidas médicas cuando estas infecciones crónicas han llegado a ser evidentes. El objeto principal y primario de esta discusión de infecciones no tuberculosas crónicas de los pulmones es recalcar la necesidad urgente de diagnosticar los estados patológicos que las anteceden, los que de otra manera conducen a una grave e incurable enfermedad; y de usar todos nuestros esfuerzos para lograr, si es posible, su erradicación pronta y completa.

REFERENCES

1 Petroff, S. A. and Schwartz, R.: "Bacteriology of Chronic Non-Tuberculous Pulmonary Infections," *Quarterly Bull., Sea View Hospital,* 6: 363, 1940-41.
2 Kline, B. S.: "Pulmonary Abscess and Pulmonary Gangrene," *J.A.M.A.,* 90:2008, 1928.
3 Kline, B. S. and Berger, S. D.: "Pulmonary Abscess and Pulmonary Gangrene," *Arch. Int. Med.,* 56:753, 1935.
4 Bucher, G. J.: "Abscess of the Lung: A Bacteriologic Study Based on One Hundred and Eighteen Cases," *Am. J. Med. Sci.,* 179:406, 1930.

5 Rona, S.: "Zur Aetiologie und Pathogenese der Plaut-Vincent Angina, der Stomacace, der Stomatitis gangrenosa idiopathica, beziehungsweeise der Noma, det Stomatitis mercurialis gangrenosa und der Lungengangren," *Arch. f. Dermat. u. Syph.*, 74:171, 1905.
6 Oliver, W. W. and Wherry, E. B.: "Notes on some Bacterial Parasites of the Human Mucous Membrane," *J. Infec. Dis.*, 28:341, 1921.
7 Greer, A. E.: "The Problem of Syphilis in a Tuberculosis Clinic," *Ann. Int. Med.*, 4:387, 1930.
8 Meakins, J. C.: "The Practice of Medicine," St. Louis, 1936, C. V. Mosby Company.
9 Greer, A. E. and Gemoets, H. N.: "The Coexistence of Pathogenic Fungi in Certain Chronic Pulmonary Diseases; With Special Reference to Pulmonary Tuberculosis," *Dis. of Chest*, 9:212, 1943.
10 Andrus, Paul M.: "Chronic Nonspecific Pulmonary Disease, Classification," *Am. Rev. Tuberc.*, 41:104, 1940.
11 Idem: "Bronchiectasis, An Analysis of Its Causes," *Am. Rev. Tuberc.*, 43:46, 1941.
12 Idem: "Chronic Nonspecific Pulmonary Disease, I. The Radiographic Diagnosis of Bronchiectasis," *Am. Rev. Tuberc.*, 41:87, 1940.
13 Idem: "Chronic Nonspecific Pulmonary Disease, II. The Pathogenesis of Bronchiectasis," *Am. Rev. Tuberc.*, 41:99, 1940.
14 Robinson, S.: "Surgery of Bronchiectasis, Including a Report of Five Complete Resections of the Lower Lobe of Lung, with one Death," *Surg., Gynec. and Obst.*, 24:194, 1917.
15 Miller, J. A.: "Subacute and Chronic Non-Tuberculous Pulmonary Infections," *Am. J. M. Sci.*, 154:805, 1917.
16 Ballon, D. H. and Ballon, H. C.: "The Diagnosis of Bronchiectasis," *Acta. Otolaryngol.*, 11:580, 1917.
17 Graham, E. A., Singer, J. J. and Ballon, H. C.: "Surgical Diseases of the Chest," Philadelphia, Lea and Febriger, pp. 576-682, 1935.
18 Singer, J. J.: "The Roentgenologic Aspects of Nontuberculous Pulmonary Disease," *Am. Rev. Tuberc.*, 38:680, 1935.

The Measurement of the Function of the Lungs*

GEORGE G. ORNSTEIN, M.D., F.C.C.P.
New York, New York

The measurement and evaluation of pulmonary function has been a difficult procedure. The common approach to this problem has been the crude method of judging pulmonary function by noting whether a subject shows evidence of dyspnea after exercise (walking up and down a ward or up a flight of stairs). This method is still the most frequent one employed in the majority of institutions where there is a need of knowing the capability of lung function.

The measurement of vital capacity is used in many places for determining pulmonary function. This method denotes only one phase of lung function, namely the ventilatory one: it is the function of bringing sufficient air into the lungs for diffusion of oxygen through the alveolar membranes into the alveolar capillary bed. This measurement of the ventilatory process does not therefore foretell the ability of the alveoli to diffuse oxygen into the pulmonary capillaries and carbon dioxide out of the capillaries into the alveolar spaces. There is therefore another phase of pulmonary function—a diffusion one. Pulmonary function therefore depends upon both a ventilatory and a diffusion phase. Before discussing methods of determining lung ventilation and diffusion of oxygen and carbon dioxide it would be logical to review some new concepts in lung ventilation and diffusion of gases in the pulmonary alveoli.

Ornstein, Herman, Friedman and Friedlander[1] stated, after investigating 170 subjects with impaired lungs, that the capability of the lungs to ventilate had no relationship to their capability to diffuse oxygen and carbon dioxide; that when ventilation was in the normal range, diffusion was usually good and only occasionally was ventilation good and diffusion poor. On the other hand, when ventilation was impaired the diffusion of oxygen and carbon dioxide had no relationship to the reduced ventilation. The above authors further stated that in subjects with marked impaired lungs and with great reduction in ventilation, diffusion of oxygen and carbon dioxide could be on a normal level. They further state the impaired lung tissues take little or no part in the ventilation and the movement of air in the lung by-passes

*Presented at the 14th Annual Meeting, American College of Chest Physicians, Chicago, June 18, 1948.

the impaired tissues and only ventilates the normal alveoli. The normal alveoli only being ventilated it is understandable to have normal diffusion of oxygen and carbon dioxide. These authors compare the expansion of the lungs to two balloons connected by means of a Y tube in a negative pressure chamber. The balloons being of equal tensile strength and the stem of the Y tube open to the atmosphere, the balloons expand equally. If the tensile strength varies the baloon with the least strength expands while the one with the greater tensile strength remains slightly distended (Fig. 1). They state that impaired lung tissue has greater tensile strength than normal lung tissue and in a similar manner does not expand while the normal lung with the lesser tensile strength is ventilated. The size of the lumen of the bronchus also plays a role in ventilation. When the lumen of the bronchus is narrowed, less air enters that portion of the lung. This is especially true when two lungs compete for air through the trachea. These same authors suggest blowing through the stem of a Y glass tube with the lumen of one of the arms narrowed. The arms are

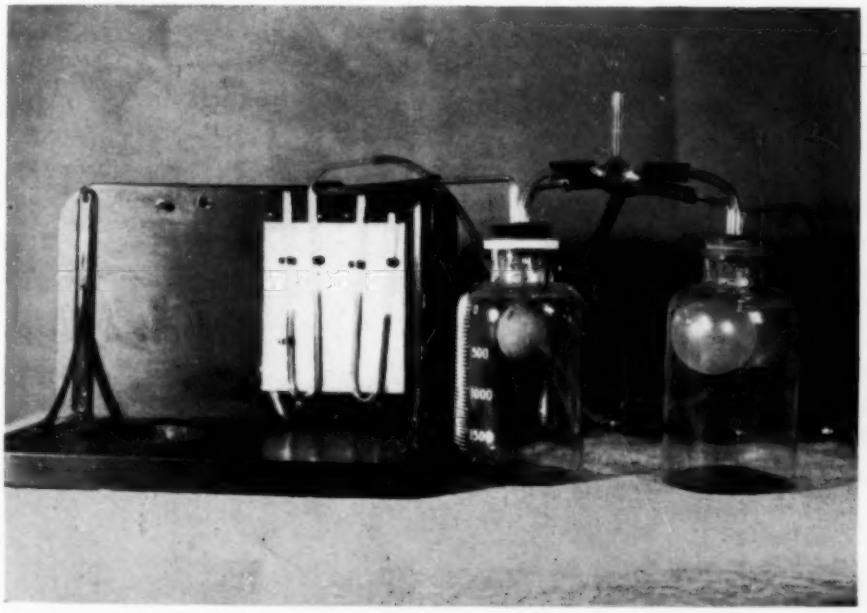

FIGURE 1: Two balloons of slightly unequal tensil strength are placed in two bottles and connected to the arms of a T tube, the vertical part of the tube being open to the atmosphere. Each flask is connected to a mercury manometer so that the negative pressure of the bottles can be measured. Through a separate opening in the rubber stopper of each bottle a tube is inserted and joined to each arm of a T tube. The negative pressure is produced with a suction hand pump through the stem tube. The pressure in each bottle is the same as can be seen by the mercury manometer. The balloon of the least tensile strength enlarges, whereas the one with the greatest tensile strength remains slightly distended.

to be placed in a beaker of water about 1 cm. below the surface. When one gently blows through the stem the air will be seen to come through the non-narrowed arm as bubbles and only an occasional one emerges through the narrowed arm. This phenomenon may be observed in patients when one of the major bronchi is partly obstructed. The air easily enters the major bronchus of the contralateral lung and distends the lung. The lung in which the lumen of the major bronchus is narrowed receives little air and expands poorly. The normal lung thus over-expands and the mediastinum shifts towards the involved lung. In expiration the reverse takes place; air rapidly flows out of the normal lung and escapes with difficulty from the involved lung which now appears to be larger than the normal one. The mediastinum shifts to the opposite side.

The bronchial tree divides in a similar manner to the trachea so that each lobule of the lung competes for air through a stem bronchiole. Therefore, besides the question of tensile strength of the impaired lung the effect of pulmonary disease on the architecture of the bronchial tree is also a factor in aeration. Ornstein, Herman, Friedman and Friedlander[1] did some interesting experimental work with balloons attached to a glass Y tube in which one arm of the Y tube had partially obstructed and the balloons placed in a negative pressure chamber. They found that the balloon with the lesser tensile strength would expand even when it was attached to the narrowed arm of the Y tube. From the above they assumed that the most important factor in ventilation of lung tissue is the tensile strength of the lung and the tensile strength of lung tissue is a much greater factor than changes in the lumen of the bronchi. Both lungs apparently compete for the air flowing down the trachea and the lung with least tensile strength obtains almost all of the air. When both lungs are of the same tensile strength air flows into both lungs. The impression of this group of authors is that even in lungs which may be considerably impaired the normal pulmonary tissue in both impaired lungs will be ventilated and will diffuse oxygen and carbon dioxide in a normal range (Fig. 2).

Pulmonary Ventilation

Pulmonary ventilation is an important phase of lung function and on its efficiency the comfort of the individual depends a great deal. The simplest ventilatory test is the measuring of the vital capacity by means of a spirometer and comparing the result obtained with the calculated vital capacity from charts based on the standing height standard, the surface area standard and the weight standard.

Ventilatory Tests

Knowing the actual vital capacity and the calculated normal vital capacity, the maximum minute ventilation of the subject on maximum effort may be predicted. Sturgis, Peabody, Francis Hall and Fremont-Smith[2] have studied the actual minute ventilation in a group of 12 young normal men. They found that these young normal men had a maximum minute ventilation of twelve times the resting minute ventilation when they rode a stationary bicycle until they were forced to stop because of complete exhaustion. During the last one and a half minutes of the ride when the exercise was most violent and the dyspnea great, the average minute ventilation of air they breathed was 60.5 liter or about twelve times the amount of air they breathed when they were lying down and at complete rest. Sturgis and his group also noted, when the maximum minute ventilation was reduced to six times the resting minute ventilation, the 12 young men could walk on level ground without any dyspnea. With this reduction in the minute ventilation, any effort of exertion, such as climbing stairs, induced symptoms of dyspnea. The dyspnea further increased as the maximum minute ventilation was decreased. Sturgis et al. worked out a formula to predict the maximum minute ventilation which was sufficiently close to the actual results obtained in their experiments. The formula is as follows:

$$\frac{\text{Actual vital capacity} \times 35}{3} = \text{Predicted maximum minute ventilation at maximum exertion.}$$

In the above formula 35 represents the average respiratory rate during the last one and a half minutes of violent exercise. The numeral 3, the denominator, represents the depth of inspiration as being one-third of the vital capacity through this last one and a half minutes of violent exercise.

Kaltreider and McCann[3] confirmed the above observations of Sturgis and his co-workers. The former investigations present a formula which they state is closer to the actual maximum minute ventilation. The Kaltreider and McCann formula is as follows:

$$\frac{41 \times \text{actual vital capacity} \times 37}{100} = \text{Predicted maximum minute ventilation at maximum exertion.}$$

Ornstein and Epstein[4] worked out a formula utilizing the actual vital capacity and calculated normal vital capacity of the subject based on the investigation of Sturgis et al. and Kaltreider and McCann, which also predicted the maximum minute ventilation on maximum exertion. Ornstein and Epstein assumed that the average normal person's maximum minute ventilation on maxi-

mum exertion was ten times the resting minute ventilation. The formula is as follows:

> Maximum minute ventilation on maximum exertion based on actual vital capacity: × : :Maximum minute ventilation on maximum exertion based on calculated normal vital capacity: 10.

X equals the number of times the maximum minute ventilation on maximum effort is greater than the resting minute ventilation. The formula may be reduced simply to:

$$\frac{\text{Actual vital capacity} \times 10}{\text{Calculated noraml vital capacity}} = \text{The number of times the maximum minute ventilation on maximum exertion is greater than the resting minute ventilation.}$$

The latter authors found that when the predicted maximum ventilation on maximum exertion was no lower than 6 times the resting minute ventilation there usually were no symptoms of dyspnea: below the above level symptoms of dyspnea increased proportionally.

Hermannsen[5] described a method of measuring pulmonary ventilation in which the subject was connected to a spirometer and was allowed to breathe into it normally for a few minutes to become adjusted to the new condition of breathing and then was made to breathe at maximum capacity as deeply and rapidly as possible for thirty seconds. This maximum breathing capacity was recorded on a drum. A Tissot spirometer could be used or a Douglas bag and the accumulated gas in the bag measured through a gasometer. Cournard, Richards and Darling[6] established the following standards for the maximum breathing capacity: the mean value for males 154 liters per minute and for females 100 liters per minute. By determining the resting minute ventilation and the maximum breathing capacity a good concept of lung ventilation can be made. Divide the resting minute ventilation result into the result of the maximum breathing capacity. The figure obtained will be the actual number of times an individual could ventilate in a minute above that of the resting minute ventilation. The above has been called the 'Ventilatory Reserve." Assuming that 7.5 liters would be the average resting minute ventilation in the normal male with a maximum breathing capacity of 154 liters, the normal ventilatory reserve would be 20 and in the normal female the ventilatory reserve would be 13. The ventilatory reserve is a very capable measurement of pulmonary function because it is based on the resting minute ventilation (which the author finds very variable: from 4 to 10 liters and very constant to each individual) and the maximum breathing capacity. If the resting minute ventilation was 5 liters in one

male and 10 liters in another but the maximum breathing capacity in both were 100 liters, in the first male the ventilatory reserve would be normal (20), and in the second male would be diminished (10).

The author has found this method of estimating lung function best and much more satisfactory and accurate than the use of the vital capacity with the prediction of the maximum ventilation on maximum exertion (See Table 1).

Pulmonary Diffusion

In 1946 Ornstein, Herman, Friedman and Friedlander[1] published a new method for the measurement of oxygen and carbon dioxide diffusion in the lungs. The above authors demonstrated that following a standard exercise test in which thirty steps are taken in a minute, normal males when connected with a rebreathing bag containing a liter of air would absorb a good portion of the oxygen in the rebreathing bag, leaving an oxygen residue of about 7.95 (‡0.851) volumes per cent. The carbon dioxide would increase to about 8 (‡O.436) volumes per cent. The above figures were the mean values in 23 normal males. In 23 normal males the oxygen volumes per cent varied from a low of 6.84 to a high of 9.5. The mean volume per cent of oxygen found in the rebreathing bag after 20 seconds following a similar standard exercise test in 25 normal females was 8.30 (‡0.74) volume per cent. The average increase in carbon dioxide was 7.70 volume per cent (‡0.497).

In utilizing this method of measuring alveolar permeability, the finding of an oxygen volume per cent up to 9.5 was considered good diffusion: any volume per cent lower, very good. A volume per cent above 10 was an indication of impairment of permeability and diffusion.

Method of estimating diffusion of oxygen and carbon dioxide:

The method was planned after the manner Plesch[7] used in determining venous carbon dioxide. A rubber rebreathing bag was fitted to a three way valve. The rubber mouth piece was attached to a tube which communicated with the room atmosphere. A turn of the three way cock connected the tube with the rebreathing bag. There is a tube leading to the rebreathing bag for the removal of samples of air.

Rebreathing Bag Assembly

Parts:

A) Mouthpiece on one arm of a three-way stopcock (Fig. 3).
B) Second arm of three-way stopcock through which the patient breathes room air during exercise period.

TABLE 1

The patients appearing in this study fall into two groups, those who came to consult because of dyspnoea and those upon whom pulmonary function tests were performed in order to determine the feasibility of thoracic surgery. This table only concerns the ventilatory function

	Sex		Age in years	Diagnosis	Dyspnoea	VENTILATORY FUNCTION V.C. *per cent*	R.M.V. *Liters*	M.B.C. *Liters*	V.R.
1	W	M	48	Pulmonary tuberc.	+	59	8.09	41.60	5.2
2	W	M	49	Pulmonary tuberc.	+	38	6.20	47.60	7.5
3	W	M	37	Pulmonary tuberc.	+	42	7.00	36.30	5.2
4	W	F	44	Pulmonary tuberc.	O	75	5.39	60.2	11.2
5	W	M	54	Pulmonary tuberc.	O	58	5.49	74.5	13.6
6	W	M	50	Pulmonary tuberc.	+	60	7.00	25.7	3.7
7	W	F	37	Pneumonectomy Congenital cystic dis., left lung	O	59	4.40	49.5	11.2
8	W	M	60	Pulmonary tuberc. Asthma Bronchiectasis	+	34	6.67	28.2	4.2
9	W	M	48	Pulmonary tuberc.	+	53	6.90	27.6	4.0
10	W	M	55	Bullae Pulmonary tuberc.	+	55	6.87	29.9	4.3
11	W	M	60	Asthma	+	51.5	4.98	20.4	4.1
12	W	M	59	Silicosis	O	69	8.50	68.0	7.9
13	W	M	57	Pulmonary tuberc.	+	58	6.98	31.3	4.5
14	W	M	47	Bronchogenic carcinoma Trumpeter	O	90	6.55	59.0	9.0
15	W	M	58	Asthma Bronchiectasis Bullae, Emphysema	+	77	6.32	42.8	6.8
16	W	M	53	Pulmonary tuberc. Thoracoplasty Emphysema	+	47	6.87	14.49	2.1
17	W	M	48	Asthma, Emphysema	+		7.99	44.3	5.5
18	W	M	52	Bullae	+		5.79	26.1	4.5
19	W	M	50	Chlorine Gas poisoning	+	78	8.72	49.4	5.7
20	W	M	50	Emphysema	+	65	6.74	62.0	9.2
21	W	M	43	Pulmonary tuberc.	+	75	5.72	68.0	11.9
22	W	M	56	Hodgkin's disease Emphysema	+	85	9.02	51.2	5.7
23	W	M	57	Cystic lung Emphysema	+	59	7.36	28.4	3.9
24	W	M	53	Bullae Bronchiectasis Chronic asthma	+	41	5.94	14.3	2.4

TABLE 1 (Continued)

		Sex	Age in years	Diagnosis	Dyspnoea	VENTILATORY FUNCTION V.C. *per cent*	R.M.V. *Liters*	M.B.C. *Liters*	V.R.
25	W	F	21	Pulmonary tuberc.	O	47	5.91	63.4	10.7
26	W	M	57	Silicosis	+	78	6.90	89.0	8.8
27	W	M	64	Emphysema	+	47	7.03	20.9	2.97
28	W	M	59	Emphysema	+	76	9.25	43.1	4.7
29	W	M	34	Bullae	+	71	6.71	27.4	4.1
30	W	M	35	Lung mass	+	29	6.64	23.1	3.5
31	W	M	72	Pulmonary tuberc.	O	71	8.01	66.2	7.29
32	W	M	48	Thoracic injury Asthma	+	45	7.97	50.6	6.4
33	W	M	70	Asthma Bronchiectasis	+	62	8.00	64.0	8.0
34	W	M	52	Emphysema Asthma	+	51	7.6	25.0	3.3
35	W	M	24	Pulmonary tuberc.	O	40	6.4	62.1	9.7
36	W	F	60	Adenoma of right lung	O	83	5.01	52.3	10.4
37	W	M	32	Reexpanded bilateral pneumothorax	O	74	6.35	88.0	13.9
38	W	M	53	Bronchiectasis	+	73	7.98	64.0	8.0
39	W	F	29	Pneumonectomy (tuberc.)	O	49	5.96	44.6	7.5
40	W	M	68	Bronchogenic carcinoma	+	97	6.65	76.8	11.5
41	W	M	21	Industrial dust case	+	76	6.49	83.1	12.8
42	W	F	38	Pneumonectomy (tuberc.)	O	39	6.30	48.0	7.7
43	W	F	53	Over-weight	O	98	4.75	93.6	19.7
44	W	M		Magenblase, Cough Expectoration	O	64	5.50	67.5	12.3
45	W	M	42	Lobectomy, left upper lobe (tuberc.)	O	90	6.75	107.7	16.0
46	W	F		Cardiac Rheumatic	+	94	5.14	62.9	12.2
47	W	M	53	Normal	O	58	5.30	66.8	12.5
48	W	M	45	Bronchogenic carcinoma left upper lobe	O	104	7.52	102.9	13.6
49	W	M	63	Primary carcinoma left upper lobe	+	96	9.16	53.4	5.8
50	W	M	48	Asthma	+	71	6.66	33.1	4.96
51	W	M	46	Bronchiectasis	O	84	7.08	97.1	13.5

TABLE 1 (Continued)

	Sex	Age in years	Diagnosis	Dyspnoea	VENTILATORY FUNCTION V.C. per cent	R.M.V. Liters	M.B.C. Liters	V.R.
52	W M	60	Bullae	+	84	6.45	73.0	11.3
53	W M	54	Silicosis	+	72	8.87	79.3	8.94
54	W M	40	Asthma	O	82	6.15	98.5	16.0
55	W M	59	Silicosis	+	76	7.06	68.0	9.6
56	W M	49	Pulmonary tuberc.	+	58	8.52	66.5	7.8
57	W M	68	Bronchogenic carcinoma	+	67	7.49	42.7	5.7
58	W M	57	Asthma	+	54	7.22	18.0	2.5
59	W M	62	Silicosis	O	78	7.95	89.4	9.5
60	W M	45	Chronic asthma	O	69	7.68	94.1	12.2
61	W F	29	Bronchiectasis	+	62	7.00	44.1	6.3
62	W F	42	Pulmonary tuberc.	+	44	5.06	22.3	4.4
63	W M	35	Pulmonary tuberc.	O	56	7.20	77.2	10.7
64	W M	54	Pulm. fibrosis	O	90	6.21	92.0	14.8
65	W M	54	Bronchiectasis	+	84	6.90	82.0	11.9
66	W M	55	Chronic asthma	+	100	9.84	77.6	7.9
67	W M	66	Bronchogenic carcinoma	+	62	6.00	64.0	10.6
68	W M	41	Bronchogenic carcinoma	O	77	6.23	113.0	18.1
69	W M	48	Chronic asthma	+	81	7.99	44.3	5.5
70	W M	53	Cystic lung	O	56	6.95	50.7	7.3
71	W M	33	Pulmonary tuberc.	O	77	8.96	88.1	9.8
72	W M	41	Bronchogenic carcinoma	O	38	6.96	78.1	11.2
73	W M	59	Bronchiectasis 20 years	O	79	5.49	89.4	16.0
74	W M	51	Pulmonary tuberc.	+	51	9.51	63.1	6.9
75	W M	49	Pulmonary tuberc.	+	51	6.4	31.4	4.9
76	W M	50	Bronchogenic carcinoma	O	71	10.3	70.9	6.9
77	W F	56	Pulm. carcinoma	+	80	5.55	34.4	6.2
78	W M	63	Pulmonary tuberc.	+	56	8.49	18.1	2.1
79	W M	56	Pulm. carcinoma	+	40	8.72	87.3	7.8
80	W M	51	Pulmonary tuberc.	+	57	9.7	60.3	6.2
81	W M	37	Emphysema ?	+	95	8.42	69.8	8.3

Abbreviations: V.C.=Vital capacity; R.M.V.=Respiratory minute volume; M.B.C.=Maximum breathing capacity; V.R.=Ventilatory reserve.

C) Third arm three-way stopcock to which the rebreathing bag (D) is attached.

E) Handle of stopcock for directing the flow of gas.

Description: (Figure 3).

A rubber rebreathing bag (D) is fitted to the lower arm (C) of a three-way valve. A rubber mouthpiece (A) is attached to the inlet of the valve. The mouthpiece can be made to communicate with the outside air through opening (B) or with the rebreathing bag through opening (C) by turning the cock handle (E).

Directions for Operation of Test:

The rebreathing bag should be thoroughly "washed" with room air, and then emptied to eliminate gases remaining from the preceding test. Turn the cock so that the mouthpiece arm communicates with the open arm (B). Add 1000 cc. of air to the bag (D) through the rubber inlet at the bottom. Clamp the inlet. The bag may be inflated with 1000 cc. of air by utilizing a basal metabolism apparatus as a metering device or by the use of a calibrated pump or piston.

Rest the subject in a sitting position for a 30 minute period.

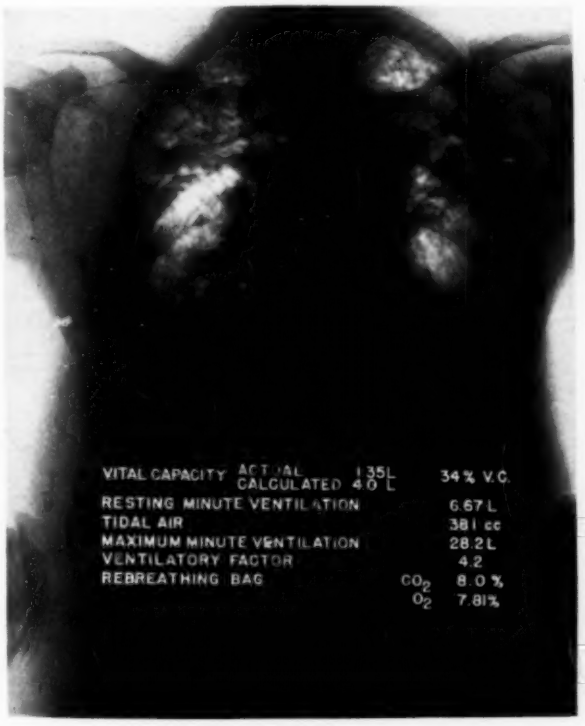

FIGURE 2

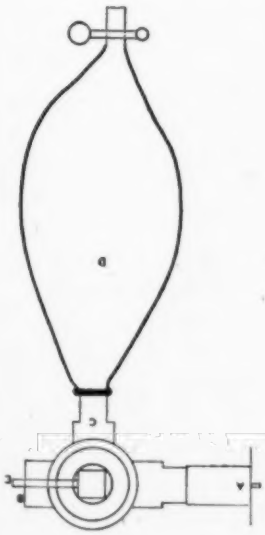

FIGURE 3

At the end of this period, place the mouthpiece in the subject's mouth and clamp his nose with a noseclip. The subject is then made to ascend and descend from an 8 inch step, thirty times in a period of one minute. Immediately after this exercise he is seated. At the end of a normal expiration the handle (E) of the cock is turned 90° to make the mouthpiece (A) communicate with the bag (D). The subject rebreathes from the bag for exactly 20 seconds. Then the cock is turned to the earlier position. The gas content of the bag is then analyzed for oxygen and carbon dioxide. The gases in the rebreathing bag are then withdrawn in the sampling tubes.

Analysis of the gases in the sampling tubes were then analyzed for oxygen by means of a Haldane-Boothby-Sandiford gas analyzer. There is a simplified (Ornstein[8]) equipment for estimating oxygen and carbon dioxide. The latter analyzer, while not as accurate as a Henderson-Haldane-Sandiford apparatus is far easier to operate. It has an accuracy of 0.1 per cent and its use can be mastered by a technician.

The following case reports demonstrate the value of a combined measurement of the ventilatory and diffusion tests.

Case 1: A white male of 55 years of age who had been under clinical observation since December 23, 1926. In 1926 he consulted the author because of a severe hemoptysis. He had an atelectatic left lung due to a healed tuberculous disease. The left lung was reduced in size and the right lung occupied most of the thorax. His sputum examinations since 1926 were negative for tubercle bacilli. From 1926 to 1947 he had frequent attacks of hemoptysis which interfered with his routine life. In 1947 a decision was made to do a left pneumonectomy.

Because of the great hypertrophy of the right lung which had been present since 1926 a question arose as to the pulmonary function of the right lung (Figure 4). There is a common belief that once a lung hypertrophies it begins to become emphysematous and rapidly does so. A pulmonary function test was therefore done. The result was as follows:

Ventilatory function:			Calculated Normal V.C.
Vital capacity	Actual	2.56 Liters	
	Calculated	4.45 Liters	58 per cent
Tidal air		745 c.c.	
Resting minute ventilation		5.49 Liters	
Maximum breathing capacity		74.5 Liters	
Ventilatory reserve		13.6	

Pulmonary diffusion:

Rebreathing bag test,

O_2	7.82 Vol. per cent
CO_2	8.05 Vol. per cent

This function test was more interesting. Firstly, note that the vital capacity was misleading. The patient seemed to have a restricted ven-

tilation. However, his ventilatory function was not reduced when you know that he had one lung functioning. A pulmonary ventilation of 13.6 is not bad. The astonishing fact was that a lung that had been hypertrophied for 21 years was able to diffuse oxygen normally.

A pneumonectomy was done in April, 1947. The patient made an uneventful recovery and has been free of symptoms since. He has been able to go back to his normal routine without any symptoms of dyspnoea.

Case 2: Case two is presented to confirm that a lung may be hypertrophied over a long period of time and not become emphysematous. A white female of 44 years had an extensive pulmonary tuberculosis involving the left lung. The tuberculous lung was collapsed with artificial pneumothorax in 1923 and the treatment abandoned after 2 years because of a complicating tuberculous empyema. The tuberculous empyema was controlled by pleural aspirations and finally in 1926 the pleural cavity became obliterated. The left lung became atelectatic and fibrotic and since 1926 the sputa have been negative for tubercle bacilli. The tuberculous disease has been in a state of arrest since 1926. The right lung has hypertrophied and remained so throughout the past 21 years.

The patient consulted the author last on March 26, 1947 concerning her pulmonary status. She had no symptoms of dyspnoea and had no complaints. The object of her visit was her concern about exercise in view of her old pulmonary tuberculosis. She had begun to play golf and she was worried whether the exercise might reactivate her old tuberculosis. She had no discomfort while golfing.

Figure 5 is a reproduction of a roentgenogram taken on March 26, 1947 which revealed an atelectatic fibrotic pulmonary tuberculosis of the left lung. The retraction of the left lung drew the heart and the mediastinum into the left thorax. The right lung had hypertrophied and also occupied a part of the left thorax. The roentgenogram was no different from the roentgenogram since 1926. The right lung had been hyper-

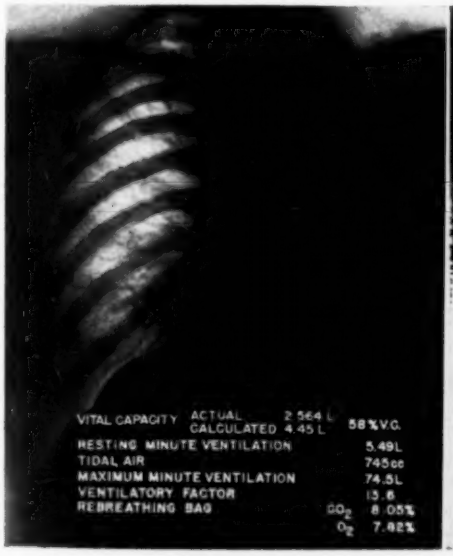

FIGURE 4

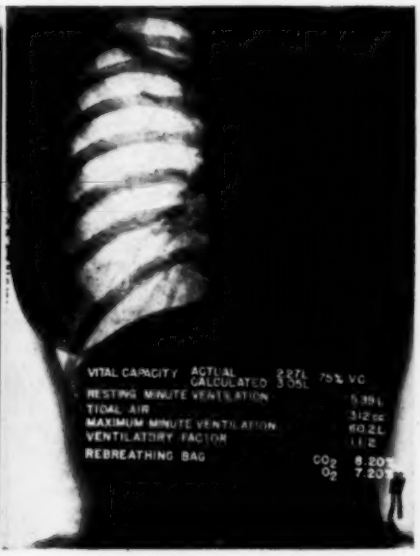

FIGURE 5

trophied for about 21 years. A lung function test was done and revealed the following:

Ventilatory function:			Calculated Normal V.C.
Vital capacity	Actual	2.27 Liters	
	Calculated	3.05 Liters	75 per cent
Tidal air		312 c.c.	
Resting minute ventilation		5.39 Liters	
Maximum breathing capacity		60.2 Liters	
Ventilatory reserve		11.2	

Pulmonary diffusion:

Rebreathing bag test,

O_2	7.20 Vol. per cent
CO_2	8.20 Vol. per cent

The right lung had been hypertrophied for 22 years. Again contrary to the prevalent impression that a lung that hypertrophies goes on to emphysema with loss of pulmonary function, this patient's hypertrophied lung has not done so. The ability of the lung to ventilate and diffuse oxygen and carbon dioxide is still within the normal range.

Case 3: A white male of 48 years had been occupied as a laborer. He had asthma since he was twelve years of age. At the age of twenty-one it had disappeared only to recur again in 1946. He stated he had a wheeze in his lungs at all times and he always had difficulty in breathing and fatigues easily on exertion. Figure 6 is a reproduction of a roentgenogram that reveals two hypertrophied lungs with exaggerated bronchial markings in both lower lobes. A pulmonary function test was done on February 1, 1947 and revealed the following:

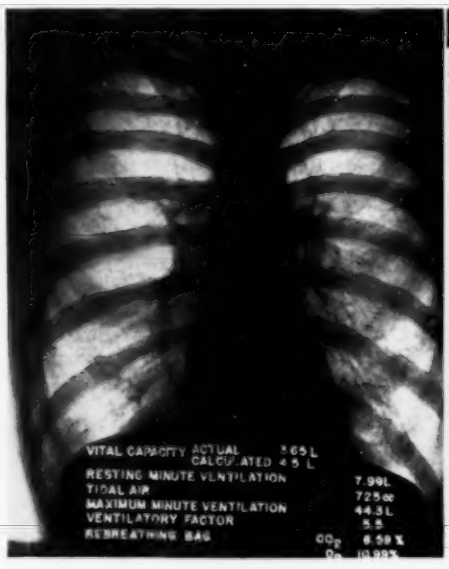

FIGURE 6

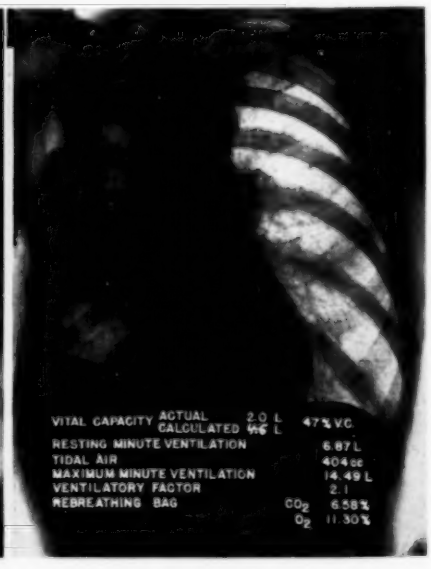

FIGURE 7

Ventilatory function:

Vital capacity	Actual	3.65 Liters
	Calculated	4.5 Liters
Tidal air		725 c.c.
Resting minute ventilation		7.99 Liters
Maximum breathing capacity		44.3 Liters
Ventilatory reserve		5.5

Pulmonary diffusion:

Rebreathing bag test,

O_2	10.99 Vol. per cent
CO_2	6.59 Vol. per cent

This case demonstrates there was both a ventilatory and diffusion disturbance.

Case 4: A white male of 54 years who had been ill with pulmonary tuberculosis since 1932. In 1934 he had a three stage thoracoplasty which controlled his pulmonary tuberculosis in his right lung. Since then his tuberculosis has been in a state of arrest. Since his operation he has been short of breath and fatigued on the least exertion.

Figure 7 is a reproduction of a roentgenogram of his thorax. The right lung had the usual shadows one sees following a thoracoplasty. The left lung was hypertrophied. A lung function test was done on September 4, 1946 and revealed the following:

			Calculated Normal V.C.
Ventilatory function:			
Vital capacity	Actual	2.0 Liters	
	Calculated	4.6 Liters	47 per cent
Tidal air		494 c.c.	
Resting minute ventilation		6.8 Liters	
Maximum breathing capacity		14.49 Liters	
Ventilatory reserve		2.1	

Pulmonary diffusion:

Rebreathing bag test,

O_2	11.30 Vol. per cent
CO_2	6.58 Vol. per cent

This patient had a very low ventilatory reserve, 2.1 times his resting minute ventilation. He also has a marked disturbance in his pulmonary diffusion as evidenced by the high volumes per cent of oxygen in his rebreathing bag (11.30 Vol. per cent).

SUMMARY

A method is given of measuring both the ventilatory and the diffusion functions of the lungs.

RESUMEN

Se presenta un método para medir tanto la función ventiladora como la función difusora de los pulmones.

REFERENCES

1 Ornstein, G. G., Herman, M., Friedman, M. and Friedlander, E.: "Pulmonary Function Tests; Discussion of Ventilatory Tests. Description of Method for Measuring Diffusion of Oxygen and Carbon Dioxide in Lungs," *Amer. Rev. Tuberc.*, 53:306, 1946.
2 Sturgis, Cyrus C., Peabody, Francis N., Hall, Francis C. and Fremont-Smith, Frank Jr.: "Relationship of Dyspnoea to the Maximum Minute Ventilation," *Arch. Int. Med.*, 29:235, 1922.
3 Kaltreider, N. L. and McCann, N. S.: "Respiratory Response During Exercise in Pulmonary Fibrosis and Emphysema," *J. Clin. Investigation*, 16:23, 1937.
4 Ornstein, George G. and Epstein, Israel G.: "Spirometry as a Procedure of Determining Pulmonary Efficiency in Pulmonary and Heart Disease: The Failure of the X-ray of the Chest in Estimating Pulmonary Reserve," *J. M. Soc. New Jersey*, August 1940.
5 Hermannsen, J.: "Untersuchungen über die maximale Ventilationsgrosse (Atemgrenzwert," *Ztschr. f. d. ges. exper. Med.*, 90:130, 1933.
6 Cournand, A., Richards, D. W Jr. and Darling, R. C.: "Graphic Tracings of Respiration in Study of Pulmonary Diseases," *Amer. Rev. Tuberc.*, 40:487, 1939.
7 Plesch, J.: "Haemodynamische Stueben," *Ztschr. f. exper. Path. u. Therap.*, 6:380, 1909.
8 Ornstein, George G.: "Simplified Equipment for Estimating the Diffusion of Oxygen and Carbon Dioxide in the Lungs," *Quart. Bull. Sea View. Hosp.*, 8:307, 1946.

Discussion

BENJAMIN P. POTTER, M.D., F.C.C.P.
Jersey City, New Jersey

The method described by Dr. Ornstein has merit even if it does nothing more than to indicate the alveolar concentration of gases. The fact that cardiorespiratory physiology is still in a rather flexible state should make welcome any new method which may clarify the subject.

As a clinician, I have been unfavorably impressed with the confusing terminology and the varied interpretations assigned to tests for pulmonary function, to say nothing of the numerous tests used and the new ones which continually are advanced for evaluation of the same problem. Before useful application of recorded studies can be made, acceptance of universal terms and coordination of the various tests should be arranged. In this respect our College can offer a much needed contribution.

Everyone has been impressed with the importance of knowing the patient's respiratory reserve prior to surgical collapse for pulmonary tuberculosis and, in more recent years, prior to excision therapy for this disease as well as for non-tuberculous conditions of the lungs. While the crude tests mentioned by Dr. Ornstein are often sufficient, retrospect observations suggest that many postoperative deaths previously ascribed to cardiac failure were,

likely, due to respiratory or cardiorespiratory insufficiency as judged from the more accurate data obtainable by present day studies of respiratory capacity.

At the same time it should be recognized that the tests do not replace careful and mature clinical judgment of the patient's ability to withstand surgery, made over a period of time as contrasted with the evaluation arrived at after one or two sittings required for the studies of respiratory function. In fact, unless one remembers that no test is free of the "psychogenic factor"—or what is more often referred to as the need for the patient's coperation—and that breathing is done under some stress connected with the artificiality of the tests, one is likely to attach too much importance to the final results. This point can be compared with the hasty unfavorable conclusion drawn, at times, by both surgeons and internists after reviewing a series of roentgenograms, clinical data, and a view of the patient at a medical surgical conference. The contrary opinion of an experienced physician who has attended the patient for a longer period of time is often of greater value.

In cases in which the respiratory reserve is borderline or poor, surgery should not be denied the patient if the attending physician's observations do not corroborate those of the physiologist. I now have a fair number of instances in which surgery was denied the patient because of physiologic studies indicating inadequate respiratory reserve, but was subsequently performed on the insistence of the clinician and resulted in effective collapse and adequate residual respiratory function.

ALVAN L. BARACH, M.D., F.C.C.P.
New York, New York

One of the things we want to know before operating on a patient is how short of breath he will be after operation, and it may well be that the test Dr. Ornstein has devised will be of considerable help. To understand the significance of the test, it would be desirable to correlate it with other observations, such as the breath-holding time. That is an extremely simple test and is of value.

The influence of anoxia on dyspnea and pulmonary ventilation, both in the normal person and the one with chronic respiratory disease is important. At an altitude of 10,000 feet there is increased pulmonary ventilation, measured carefully by Engel and Ferris, increasing every 2,000 feet. In patients with respiratory disease

such as pulmonary emphysema, it is often of great help to determine their respiratory function, to test the volume of breathing, to determine the difference between breathing air and breathing oxygen. A man breathing 12 liters a minute may, within five minutes of breathing 100 per cent oxygen, reduce his ventilation to 8 to 10 liters per minute. This gives a considerable clue to that particular person's dependence upon oxygen.

Even though the arterial oxygen saturation may be at that time 95 per cent, it is a misunderstanding to say that lack of oxygen or anoxia or hypoxia is not involved, simply because his oxygen saturation is normal or nearly so. It is evident that these people are making sufficiently burdensome efforts to ventilate their lungs to give them dyspnea and acute distress, and this increased ventilation happens at times to result in saturation that is almost normal. However, in almost 95 per cent of patients with hypertrophic pulmonary emphysema, there is marked reduction in pulmonary ventilation after four days inhalation of a 50 per cent oxygen atmosphere. We may think of dyspnea in chronic respiratory disease as a combined effect of: (1) increased ventilation; (2) the capacity of the individual to provide this increased ventilation without distress and (3) the capacity of the individual to maintain a normal hemo-respiratory exchange.

It will be of considerable interest and profit to us to watch the further observations of the diffusion method of Dr. Ornstein. I should like to ask him whether he has been able to separate diffusion through the lung parenchyma, through the pulmonary capillaries, from diffusion within the lung itself. We know that irregular ventilation of the alveoli takes place in pulmonary emphysema. There are sometimes large dead spaces in which failure to absorb oxygen does not come from impairment of the pulmonary capillaries, but from waste spaces where air is present, not exposed to the capillaries at all. There are of course many other factors that are important, such as the difference in ventilation before and after inhalation of bronchodilators; the degree with which many patients with chronic pulmonary disease fail to use the diaphragm although they are partly able to do so. In periods of distress, naturally the costal and neck muscle respiration predominates. The pulmonary ventilation may be high. But many of these people can be taught to use the diaphragm, which they have forgotten to use because of the panic brought on by extreme dyspnea. With diaphragmatic breathing the maximal pulmonary ventilation may increase.

I am now making a plea to correlate the tests we have already learned with the new tests so interestingly presented to us this morning.

EDWIN R. LEVINE, M.D., F.C.C.P.
Chicago, Illinois

It is notable that physiology is beginning to come out of the laboratory into clinical medicine. Work which can be done only by highly trained research individuals, has clinical value only by indirection. When a physiologic technic can be made available to any hospital, to any clinical group, then that technic begins to have clinical importance. The work presented today shows how we can think in terms of doing physiologic testing even as we do blood testing and x-ray.

We should remember that decompensation and disability of patients does not always come from damage to the lung, or does the lack of such disability always indicate lung function. We are aware of the fact that emphysematous patients do not have slowly developing disability, but go along for some time and then suddenly, by some mechanism or some intercurrent infection, show marked change and disability; and the disability frequently continues and is progressive. It sometimes impresses me like stepping off the roof of a building; one day a man seems able to do his work, and two or three days later he is completely disabled. It appears to be a breakdown in the compensatory mechanism rather than marked change in the lung function itself.

GEORGE G. ORNSTEIN, M.D., F.C.C.P.
New York, New York

In reply to Dr. Barach I would like to say that for the past four years at Sea View Hospital and the Metropolitan Hospital every patient who had a problem of dyspnea has gone through this test. We are now doing these tests at Halloran Hospital and at my office, and thus are accumulating hundreds of cases. It is not just a question of a small group. We would not consider thoracic surgery unless the patient had a good diffusion test. We are willing to go along with lower ventilation but not with poor diffusion. Any doctor associated with a large institution where much thoracic surgery was done would know of a large number of physiologic cripples who had recovered from their disease but who, after surgery, had never been able to walk far from their chairs. Whether or not pulmonary surgery should be done in such cases is questionable.

One interesting thing we have learned, particularly in pneumonectomies, of which we have done many at Sea View, is that a thoracoplasty following pneumonectomy cuts down the ventilation markedly. Inasmuch as we believe that the remaining lung

may hypertrophy and not become emphysematous, it is wiser to allow that lung to take up the whole thorax and it may ventilate and diffuse better than by restricting the thorax with thoracoplasty after pneumonectomy. This year we are attempting to use the diffusion test in bronchospirometry. We started the work at the Metropolitan Hospital, where we are trying to create an oxygen debt with an arm weight exercise. In bronchospirometry the other day we had a patient with a good diffusion test. We knew by our fluoroscopic studies that one lung was doing most of the functioning, and we had the usual picture of one lung ventilating poorly and the other doing most of the ventilation. The amazing thing was that in both lungs, in spite of the variation in ventilation, the oxygen equivalent was about the same; about three liters. In bronchospirometry, under resting conditions, unless an oxygen debt is produced, the lung that ventilated poorly but apparently diffused well, might have shown its permeability defect could we have produced an oxygen debt.

Dr. Barach brought out an interesting question of irregular ventilation and irregular diffusion in parts of the lung which do not ventilate. The above surprised us more than anything else. We took a group of normal individuals who had normal diffusion tests and cut down their ventilation by putting them in canvas jackets, thus reducing the ventilation. We had one man strapped down to 25 per cent of his normal vital capacity, yet the diffusion tests were exactly alike whether the ventilation was good or poor. So the two systems of ventilation and diffusion have no relationship. Usually where there is good ventilation there is also good diffusion, but we have had cases where ventilation was good and diffusion poor. On the other hand no matter how low the ventilation there may be good diffusion. Whether the small area of lung tissue being ventilated is sufficient under effort to supply the entire blood stream with oxygen is hard to say. Unfortunately, when a patient has a great deal of anoxia no physiologic test is needed; you can see it with your eyes. But as a rule people with impaired diffusion and ventilation are comfortable when at rest, and if diffusion tests are done at that time and compared to normal, without developing an oxygen debt, they will be found pretty close to normal. One cannot know the capability of the lung to diffuse oxygen unless an oxygen debt is produced.

GEORGE E. WRIGHT, M.D.
Saranac Lake, New York

I think it might clarify things somewhat if Dr. Ornstein would tell us what he means by ventilation. There is as yet no un-

animity in the way we use these terms. When I speak of ventilation I mean the distribution of gases in the lung. For example, whether a room is well ventilated depends on the amount of fresh air that comes into the room and, equally important, how it is distributed. If I understand Dr. Ornstein correctly, he means simply the amount of air moved into and out of the lung. It is not surprising that Dr. Ornstein finds no change in the diffusion test when he straps the chest. After all, he has not changed the efficacy with which the lung can be ventilated by simply strapping the chest; all he does is reduce the maximum ability of the respiratory apparatus to move air in and out of the lung. So long as the subject can still move the required one liter back and forth, there should be no evidence of abnormality in the test.

I am delighted that Dr. Ornstein has simply ignored certain *a priori* objections to this method and proceeded with these studies, because information has been brought out that is of use. I think, however, that Dr. Barach's comment regarding the necessity of corelating a test with other things is apropos, particularly with regard to Dr. Ornstein's work. I am loath to accept this as a method for testing diffusion across the membranes until he can show that it correlates well with a measured abnormal oxygen and CO_2 tension in the blood during exercise. It would be of interest also if he would tell us how many cases he predicted would do poorly and which he subsequently found did so when operated upon.

I should like to know how many cases were operated upon that Dr. Ornstein said should not be operated upon, and of these how many turned out well and how many turned out poorly.

In our experience we have not been particularly keen to have operations on emphysematous patients. But we have found to our pleasant surprise—at least in 10 or 12 cases—that the surgeon can operate successfully on persons with severe emphysema if the operation is done in small stages; at times they have done one rib at a time. The emphysematous patient does not tolerate well a soft chest wall in the immediate postoperative period; but if the area is kept small many patients with emphysema can be carried successfully through a surgical procedure.

Dr. Barach's comment on hypoxia points out the difficulty of making oneself clear. I certainly do not deny that hypoxia will drive the respiratory center in abnormal fashion; I know it will. The point I wish to make is that it does not always do it. The variations in sensitivity of the chemo receptors to oxygen are well known. There is a difference between the reactions of a group of normal persons suddenly exposed to low oxygen tensions, and a group of patients who have lived with hypoxia for one, three

or four years. Some patients are able to go around with arterial oxygen tensions as low as 60 mm. of mercury, and hemoglobin saturation as low as 85 per cent, and when measured for ventilation response during exercise, they show no abnormality. I think one is forced to conclude from such studies that hypoxia does not always produce hyperventilation.

One other point should be considered; it is difficult to divorce the physiology of the circulatory system from that of the respiratory system. And the effects of poor blood supply to the tissues cannot be ignored in making studies of pulmonary function. Until better ways are devised for studying the circulatory and the respiratory system, this confusion will exist and many curious findings will occur.

GEORGE G. ORNSTEIN, M.D., F.C.C.P.
New York, New York

With the presentation of any new work, other investigators usually are skeptical only because they are not familiar with the new work and are hesitant to accept it. Is it not likely that when a new test for pulmonary function is reported in the literature, other investigators will repeat the work and either prove or disprove it? My group has presented these studies in the literature over the past few years and up to this time there has been no disconfirmation of our efforts. On the other hand, the tests have been applied clinically in all cases to have thoracic surgery at Sea View and Metropolitan Hospitals, and have been of great assistance in the selection of patients. Dr. Wright stated that we should do the oxygen volume per cent of the blood in conjunction with our rebreathing bag test before he could accept our work. However, up to the present time no one has reported any work disproving our claims for the value of the test.

We are now doing the gas volume percentage of the blood in conjunction with the rebreathing bag tests. This was not possible until we had the technical help that can accurately use a tenometer, with which few technicians are familiar. Our results on this will be reported in the near future. It was necessary to work out a new exercise test; the step exercise test could not be used as our samples of blood are taken from the femoral artery. With the development of a new exercise test in the recumbant position so that we could use an indwelling catheter in the femoral artery, we have had to establish new controls. The basic work has been completed and we will now be able to report the oxygen volume per cent in the rebreathing bag and in the femoral artery occurring at the same moment.

Up to the present time we have done many hundreds of function tests and the patients, following operation, have shown that the tests have prophesized that they would not be pulmonary cripples so far as pulmonary function is concerned.

GEORGE E. WRIGHT, M.D.
Saranac Lake, New York

In general I do not like to discuss a method that I have not used personally. In our laboratory we try to study carefully all aspects of any method we devise before we make any statements concerning it. It is unusual for an investigator to publish a method without determining at least the elementary and fundamental controversial aspects of the procedure. It is indeed a new trend to expect others to do it for him.

There is no question about Dr. Ornstein's factual findings, namely, that oxygen tension did not drop as low in some of these cases during rebreathing as it does in others. The interpretation is the point, I think, upon which we differ. He has not, for example, shown us any evidence wherein he has controlled the size of the lung at the time the man is turned into the rebreathing bag. From a mathematical standpoint one can calculate that in a man with a large mid capacity the result that should be obtained with his method is exactly what he actually does get, and it has absolutely nothing to do with the passage of oxygen across the alveolar membrane. In other words, he starts out, in people with emphysema, with a large total volume of air to breathe in 20 seconds than he does in the normal man; therefore, given the same amount of oxygen consumed per minute, he must end up with a higher oxygen tension in the rebreathing bag of the emphysematous patient. I think the method should be considered as one for study of lung volume rather than for diffusion of oxygen or CO_2 across membrane. The method may have some use when it is properly correlated with other factual data; until that is done, however, it cannot be accepted without some reservation.

ALVAN L. BARACH, M.D., F.C.C.P.
New York, New York

I think one observation might clarify what I think is a somewhat confused point in this discussion. When we speak of ventilation of the lung, are we speaking of just the amount of air that goes in and out of the lung, or are we speaking also of alveolar ventilation? Just compressing the chest does not duplicate what

happens in the patient with pulmonary fibrosis and pulmonary emphysema. The lung volume and ventilation of the patient with pulmonary emphysema may be markedly changed by manually elevating the diaphragm. Pushing up the diaphragm 10 times during expiration, particularly after inhalation of a bronchodilator substance, increases the vital capacity 1,000 cc. a minute and a half afterward. The patient's sensation of dyspnea may have disappeared. He had been breathing a high pulmonary ventilation, he had had a large volume of air (high residual air) with which to dilute any gas, but his alveolar ventilation was poor.

I think it would be interesting to Dr. Ornstein and to Dr. Wright, and to myself, to do this test after manual elevation of the diaphragm, i.e., get the per cent CO_2 and oxygen in the bag when a man has an overfilled lung, and then squeeze out 800 or 1,000 cc. of air and see what the chest shows afterward.

I am sure that you cannot in this test separate the effects of diffusion of air within the lung alveoli, particularly in the damaged lung, from diffusion across the capillaries; large areas of emphysematous lung are irregularly inflated; sometimes five minutes may pass before some area opens up. In other words, in the test there are two factors; one is diffusion of air within the lung itself, particularly in cases of emphysema, and the second factor is the diffusion of gases across the pulmonary capillaries. These two separate functions are included in the test as I see it; total pulmonary ventilation may also be high with poor alveolar ventilation.

Comments on Bacterial Resistance to Streptomycin*

ARNOLD SHAMASKIN, M.D., F.C.C.P., F.A.C.P.**
Hines, Illinois

Shortly after streptomycin was introduced in the treatment of tuberculosis, two major obstacles to its value as a therapeutic agent became apparent. These were, vestibular damage and development of bacterial resistance. With the reduction in the daily dosage from 2 gm. and higher, to 1 gm. and later to 0.5 gm., serious vestibular damage has been eliminated. However, development of bacterial resistance, which is apparently due to duration of treatment rather than to dosage, remains for the present the most serious threat to successful streptomycin therapy in tuberculosis. With the appearance of resistant forms of tubercle bacilli, streptomycin ceases to be an effective therapeutic agent not only for the individual patient but also for those to whom he may transmit the disease.

Youmans and Williston[1] found that when a group of mice were injected intravenously with 0.1 mg. of a culture of tubercle bacilli isolated from a patient with pulmonary tuberculosis, streptomycin had a marked suppressive effect on the infection produced in the animals. On the other hand when a group of mice were injected in the same manner with a culture of tubercle bacilli from the same patient after he was treated with streptomycin, the infection resulting from it was uninfluenced by the drug.

Bogen[2] related the case of a nurse who contracted tuberculosis while working with streptomycin treated patients. Tubercle bacilli recovered from this case were resistant to 1000 micrograms per cc. on original isolation.

It is obvious why the study of bacterial resistance to streptomycin and specifically the search for measures to prevent it are occupying a very prominent place in this field of investigation.

The theory behind the development of bacterial resistance to streptomycin is based on the knowledge that probably every case of tuberculosis harbors different varieties of tubercle bacilli. By

---

*From the Tuberculosis Service, Veterans Administration Hospital, Hines, Illinois. Published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the author.

**Chief, Tuberculosis Service.

far the vast majority of organisms are sensitive to streptomycin but an occasional form is by nature resistant to the drug. It is undoubtedly for this reason that a favorable initial response to streptomycin is shown by almost every patient who has active and progressive tuberculosis and is not moribund and that, if treated long enough, probably every case acquires resistance to streptomycin sooner or later.

It may be reasoned that under streptomycin therapy all the sensitive organisms are inhibited and are either prevented from multiplying altogether or their rate of repreduction is greatly reduced. Thus the army of invaders becomes reduced at a fairly rapid rate when exposed to the drug. While the vast number of sensitive organisms are thus held in check by streptomycin, the natural defensive forces of the body come into play, assume dominance, and begin to recover lost ground. It is apparent then that the time during which effective use of streptomycin can be made is limited to the minimum time required by the streptomycin resistant organisms to increase in sufficient numbers to become a potent force against which streptomycin is a useless weapon.

No relationship has been found to exist between the degree of sensitivity of tubercle bacilli to streptomycin and the degree of their virulence. Either variety may be of high or low virulence. Both varieties work hand in hand and each contributes its share to the clinical picture in proportion to its numerical strength as well as to degree of virulence.

The rationale of the various methods proposed for combating the development of resistance is predicated upon the speed with which the enemy must be overcome. In other words this must be a "blitz" campaign which would enable the patient to overcome the disease in the shortest possible time before the streptomycin resistant organisms can multiply sufficiently to become effective and to take over the situation.

Since resistant strains of tubercle bacilli usually begin to make their appearance before the end of the second month of treatment, shorter periods of treatment than 60 days have been advocated and are being tried. Simultaneously other drugs such as promizole and para-aminosalicylic acid are being investigated for the value they may have as auxiliary weapons against the tubercle bacilli, with the hope that they may act on the resistant forms when administered in conjunction with streptomycin.

It is also hoped that further research may bring forth other antibiotics which could be used for the treatment of tuberculous patients whose organisms have become resistant to streptomycin.

Meanwhile a plea is made against the indiscriminate use of streptomycin as a so-called "additional boost" for the treatment

of comparatively mild tuberculous lesions which are very likely to regress or have already shown evidences of satisfactory regression both clinically and roentgenologically under adequate conventional therapy. Abuse of the drug may deprive the patient of its benefits should he ever need it more urgently. It also helps to perpetuate in the community a form of tuberculosis on which streptomycin has no effect. While administering to the individual patient, the public health interests must not be lost sight of.

REFERENCES

1 Youmans, G. P. and Williston, E. H.: "Effect of Streptomycin on Experimental Infections Produced in Mice with Streptomycin Resistant Strains of M. Tuberculosis Var. Hominis," *Proc. Soc. Exper. Biol. and Med.*, 63:131, 1946.

2 Bogen, Emil: Report During Round Table Discussion on "Dosage of Streptomycin" at Fourteenth Annual Meeting, American College of Chest Physicians, Chicago, June 20, 1948.

Extrapleural Pneumothorax*

LOUIS L. FRIEDMAN, M.D., F.C.C.P.,
L. ORTON DAVENPORT, M.D., F.C.C.P. and
JOSEPH C. BOHORFOUSH, M.D., F.C.C.P.
Birmingham, Alabama

Introduction: In the past ten years or so numerous conflicting reports have appeared in the medical literature concerning the efficacy and value of extrapleural pneumothorax in pulmonary tuberculosis. After Graf and Schmidt[1] in 1936 and 1937 published their very favorable results obtained with this form of temporary collapse therapy, there was an almost immediate world-wide manifestation of renewed interest in the procedure originally described and developed by Tuffier[2] many years previously. The initial wave of favorable reports from the pens of enthusiastic advocates, however, was soon followed by equally numerous and authentic unfavorable reports by the critics of this procedure. As a result of these conflicting opinions, extrapleural pneumothorax, today, occupies a very questionable and controversial position in the phthisiologist's therapeutic armamentarium.

This study was undertaken in order to present a statistical analysis of our own experiences and results with this form of collapse therapy in a large series of cases. We trust that this evaluation will help to classify the procedure correctly and not add to the existing confusion. All of the cases used in this report are from Jefferson County Tuberculosis Sanatorium and all the surgery was performed by Dr. L. O. Davenport.

Materials (Table I): From October 1939 through December 1946, a total of 141 patients had extrapleural procedures performed at the Jefferson County Tuberculosis Sanatorium. In selecting cases for study only 97 were considered satisfactory for evaluation. The remaining 44 patients are not included in this study as the available data in these cases was considered insufficient or unsatisfactory for meaningful evaluation. Bilateral extrapleural pneumothorax was established in 4 of the studied cases (figure 2) while 3 other patients in this group had two-stage extrapleural pneumothoraces (figure 7). One hundred and four extrapleural procedures are therefore available for this study. In 7 of the cases studied the extrapleural pneumothorax was combined with a

*From the Jefferson County Tuberculosis Sanatorium, Birmingham, Alabama. Presented at the Thirteenth Annual Meeting of the American College of Chest Physicians, June 5, 1947 at Atlantic City, New Jersey.

preexisting intrapleural pneumothorax (figure 6). Twenty-four of the extrapleural spaces were maintained with oil (figures 1, 2).

Operative and Immediate Post-operative Technique: The simple pre-operative preparations include a saline enema, a barbiturate and a mild hypnotic prior to surgery. The patient is then placed

TABLE I

Cases Followed	97
Cases not Followed	44
Total Number of Cases	141
Total cases available for study	97
Bilateral extrapleural pneumothorax	4
Two-stage extrapleural pneumothorax	3
Total extrapleural procedures followed	104
Total extrapleural procedures not followed	44
Total	148

MISCELLANEOUS

Combined intra and extrapleural pneumothorax (one accidentally)	7
Collapse maintained with oil	24

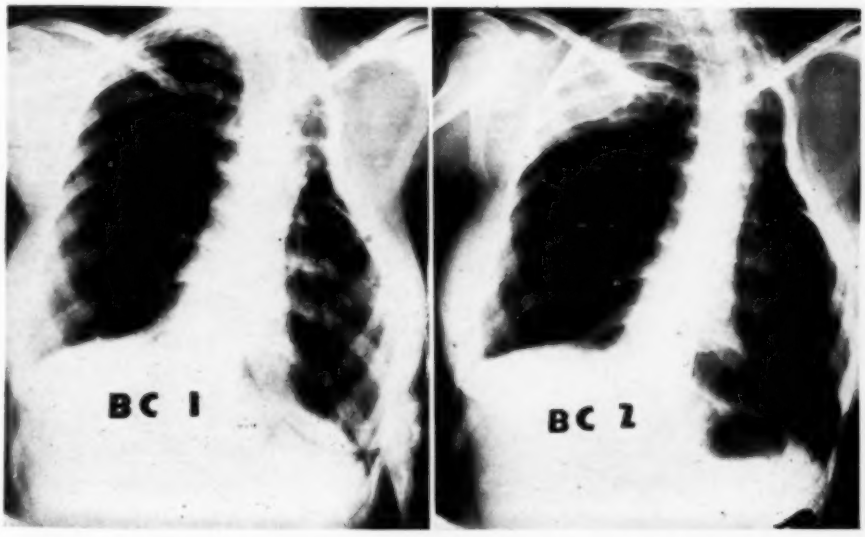

FIGURE 1: B. C., a 26-year-old white female. Had thoracoplasty on left side following which a large thin-walled cavity developed on the right side (1). Could not establish intrapleural pneumothorax on right side and thoracoplasty was not possible because of patient's generally poor condition. Extrapleural pneumothorax was established on 2-12-42. Converted to oleothorax in 1944 when patient could no longer manage to arrange for air refills. Sixty-five months later (2) the disease was completely arrested and patient was enjoying a practically normal existence.

FIGURE 2: G. M., a 27-year-old white female. Intrapleural pneumothorax had failed on both sides (1). Patient was very uncooperative. Left extrapleural pneumothorax established on 3-14-46 (2), followed by right extrapleural pneumothorax (3). Left converted to oleothorax when patient left sanatorium against advice of physician. Sixteen months later (4) patient is making good progress. Since leaving the sanatorium has managed to contract syphilis in addition to pulmonary tuberculosis.

on the operating table in a lateral position, the same as is normally used for thoracoplasty. All cases in this series were performed under local anesthesia (novocaine 1 per cent). Since 50 per cent or more of the lung is collapsed in a few minutes time, there is always some secretion expressed from the collapsing lung. With novocaine anesthesia patients are able to cough and expectorate several times during the operation which normally lasts 30 to 40 minutes. After infiltration of the skin, subcutaneous tissue and regional muscles is accomplished with the anesthetic agent, a linear incision 10 to 12 centimeters long is made midway between the spine and the mesial border of the scapula, and extended down to the ribs. The intercostal nerves supplying the surgical field are blocked with a 1 per cent novocaine solution. The posterior serratus muscle is then freed from its attachment to the fourth and fifth ribs and retracted. This muscle is often of great value in effecting an air-tight closure. Seven to eight centimeters of the fourth rib is resected periosteally. Through the rib bed the extrapleural fascia is separated and the extrapleural space developed. The separation is extended as far as possible with the finger. Then the lung is depressed with an Overholt lighted-retractor and the separation continued with hard gauze sponges on long curved forceps. During this part of the operation great diligence must be exercised to avoid tearing the pleura.

We have found that the collapse obtained will not be adequate or satisfactory unless the extreme apex is separated from the dome of the pleural cavity. The dissection on the mediastinal surface is carried to the arch of the aorta on the left and to a comparable level on the right. On the posterior, lateral, and anterior pulmonary surfaces the separation is extended downward to well below the diseased area. Before closing, the extrapleural pocket is inspected carefully for bleeding points. These can usually be controlled by hot saline packs. Occasionally, a persistent bleeding vessel requires the application of one of the newer hemostatic agents such as thromboplastin. The periosteum and intercostal muscles are approximated by a continuous suture of chromic O catgut, and the posterior serratus muscle is drawn over and fixed to reinforce the suture line. Finally, the trapezius and rhomboid muscles and fascia are closed by a continuous suture of catgut, and the skin is repaired with silk.

At the end of the operation a pneumothorax needle is inserted into the newly established extrapleural space. Usually, a neutral reading is recorded and air is injected until a manometric reading of approximately +6 cm. of water is obtained. About 8 hours later, a second refill is administered until the extrapleural pressure is raised to +8 cm. of water. Twenty-four hours later the

FIGURE 3: J. I., a 30-year-old white male. Condition hopeless (1). Left extrapleural pneumothorax established 1-9-41, with good results (2). Followed by thoracoplasty on right. Disease arrested and patient doing very well 78 months later (3).

pressure is increased to +12 cm. of water. Following this refill, air is administered every 3 to 4 days during the immediate postoperative period.

A serosanguineous exudate always develops in the extrapleural space but no attempt is made to aspirate this fluid until the sixth or seventh postoperative day. At this time, the patient is seated in an erect position and aspiration is performed with a 15 or 16 gauge needle, 2½ to 3 inches long, through the second interspace. To avoid future complications, the extrapleural space should hereafter be kept as dry as possible with frequent aspirations until no fluid reforms. If the fluid continues to remain very sanguineous, the extrapleural space is washed with isotonic saline solution when necessary.

In order to maintain the maximum and necessary amount of therapeutic collapse, it is necessary to maintain a positive pressure in the extrapleural space at all times. If the pressure accidentally becomes neutral or negative between refills, the space will gradually be obliterated. At the end of two weeks of gradually increasing positive pressure in the extrapleural space, patients usually will tolerate a closing pressure of +24 to +30 cm. of water. The degree of positive pressure obtained in the extrapleural space usually determines the frequency of refills.

Distribution of Cases Followed by Color, Sex and Age (Table II): Of the 97 patients 81 were white and only 16 were negroes. Although the white inhabitants of the sanatorium outnumbered the negroes, the latter discrepancy cannot be explained on this basis. Rather, it is felt that the condition of the negro patients who were successful in gaining admission to the sanatorium was generally so hopeless that not many were actually candidates by any standards for this type of surgery. Sixty-seven (69 per cent) were female and 30 (31 per cent) were males. This difference is

TABLE II

Distribution of Cases Followed by Color, Sex and Age

Age Groups	WHITE (81) Male 29.9 Pct.	WHITE (81) Female 70.1 Pct.	COLORED (16) Male 37.5 Pct.	COLORED (16) Female 62.5 Pct.	TOTAL (97) Male 31 Pct.	TOTAL (97) Female 69 Pct.
10-19	2	4	0	1	2	5
20-29	6	*27*	3	6	9	*33*
30-39	*13*	*17*	1	2	*14*	*19*
40-49	2	7	1	0	3	7
50-59	1	2	1	1	2	3
Total	24	57	6	10	30	67

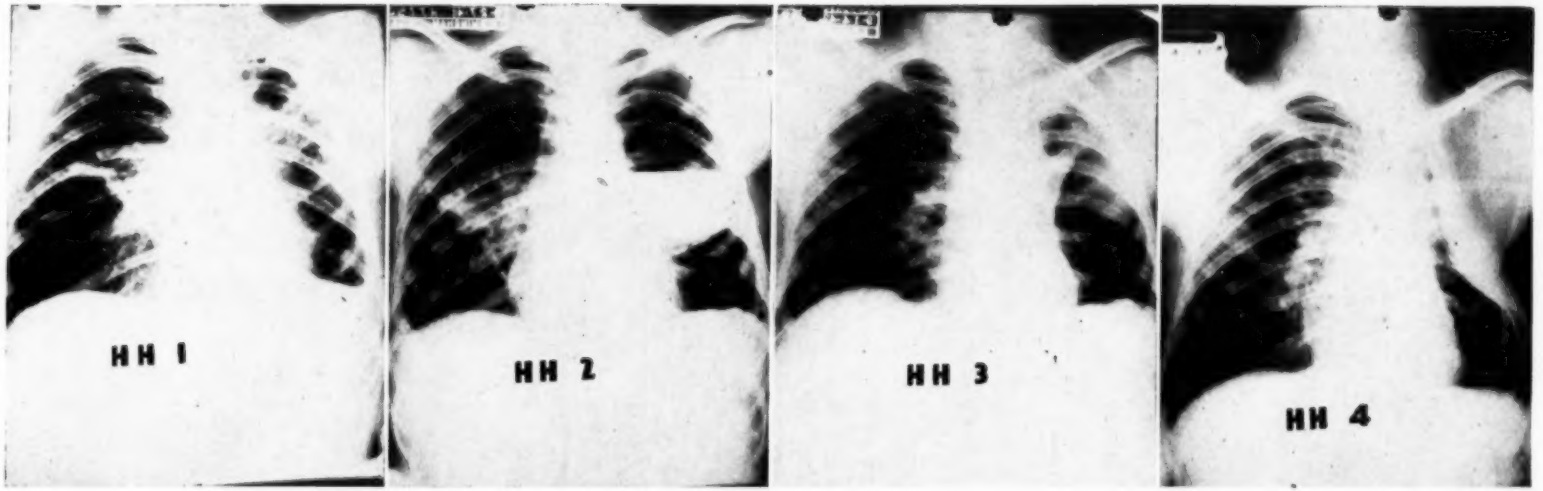

FIGURE 4: H. H., a 31-year-old white male. In hopeless condition. Bilateral far advanced exudative-cavernous disease. Right intrapleural pneumothorax in progress. Left failed (1). Extrapleural pneumothorax established 9-4-41 (2). Right side reexpanded following improvement. Extrapleural pneumothorax unsatisfactory but halted progress of disease in left lung (3). Thoracoplasty performed on left side. Sixty-nine months later disease arrested and patient engaging in useful activity (4).

attributed to two main reasons. For one thing, cosmetic considerations prompted females to accept this procedure in preference to a deforming operation such as a thoracoplasty, even when the latter was actually the procedure of choice. In addition, there is some discrepancy in the sanatorium population ratio which favors the females. The youngest patient in this series was a 14 year old colored female while the oldest was a 58 year old male. The former died within 8 months after surgery, and in the latter case the operation failed because a dense pachypleuritis made the procedure impossible. More than half of the patients were from 20 to 39 years of age. In view of the usual age distribution in tuberculosis sanatoria and for tuberculosis in general, the latter observation has no particular significance.

Indications for Extrapleural Procedure in Group Followed (Table III): Only after a fair trial of intrapleural pneumothorax and bed rest had failed to control the disease was any patient in this group considered as a possible candidate for extrapleural pneumothorax. In addition, many had had unsuccessful phrenic nerve operations. Forty-three (41.3 per cent) of the procedures were performed in hopeless cases (figures 1, 3, 4 and 7). The nature of the disease or the condition of the patient in these instances was such that thoracoplasty was beyond reasonable consideration. Twenty-nine (27.9 per cent) procedures were performed as the surgeon's choice (figure 9). The bulk of the cases in this classification were selected early in the series when the numerous enthusiastic and favorable reports actually led the surgeon as well as the patient to believe that the procedure was preferable to thoracoplasty (figure 2). In some of these instances extrapleural pneumothorax was established as a preparatory measure for future thoracoplasty (figures 3 and 4) on the ipsolateral or contralateral side. In recent years this situation has more than reversed itself and only very few are performed in preference to thoracoplasty while many more are established in preparation

TABLE III

Indications for Extrapleural Procedure in Group Followed

		Total	Per Cent
1. Hopeless		43	41.3
2. Surgeon's Choice		29	27.9
3. Patient's Choice		32	30.8
a) Refused thoracoplasty	*17*		
b) Cosmetic reasons	*15*		
	Total	104	100.0

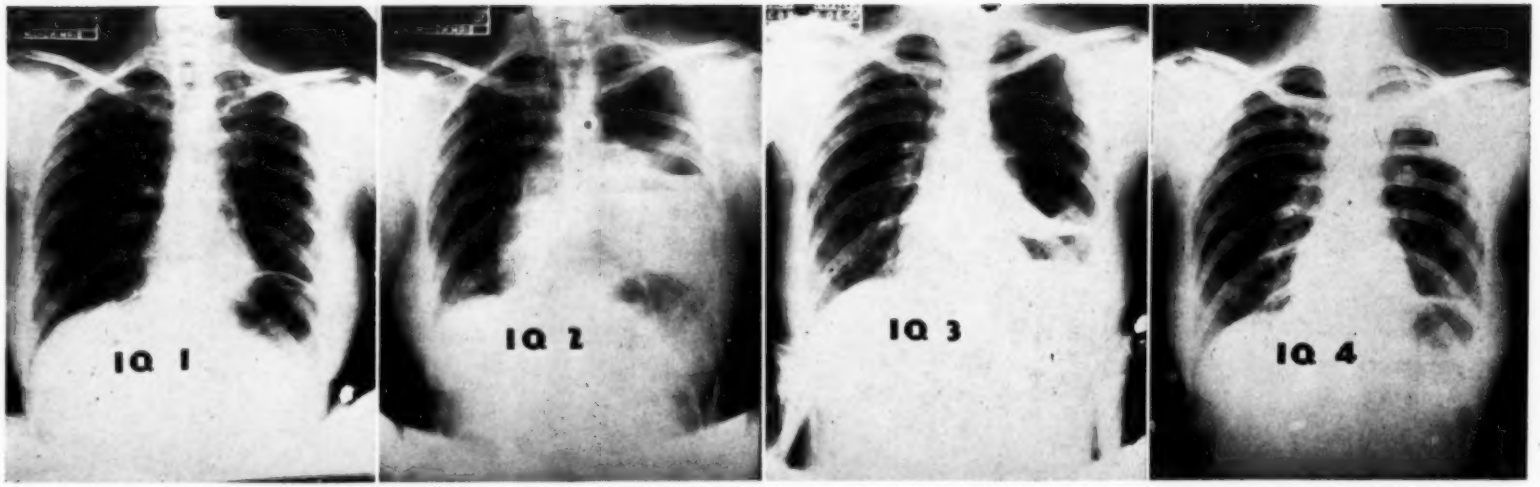

FIGURE 5: I. Q., a 28-year-old white female, left and right intrapleural pneumothorax and left phrenic nerve crush failed to control disease. Refused thoracoplasty because of fear and cosmetic considerations (1). Extrapleural pneumothorax established 10-2-39 (2). Notice immediate postoperative fluid and emphysema in subcutaneous tissues of neck. Four weeks later (3) fluid almost completely reabsorbed and a successful extrapleural space achieved. Ninety-two months later the lung is reexpanded (4), disease is arrested and patient is in excellent health.

for future thoracoplasty. Extrapleural pneumothorax is an excellent temporizing and preparatory measure for a possible future thoracoplasty. Preparatory extrapleural pneumothorax by temporary control of the pulmonary disease and fixation of the mediastinum in many cases (figure 4) insures the maximum therapeutic benefits which may be expected from an eventual thoracoplasty. Many patients who otherwise would be left at the mercy of a progressive and fulminating disease can be benefited by utilizing extrapleural pneumothorax in this fashion. The remaining 32 (30.8 per cent) of the procedures were performed as the patient's choice (figure 5). Some had read glowing newspaper accounts reporting the success of extrapleural pneumothorax as a collapse measure, and others were influenced by the very fear of surgery and prolonged convalescence involved in accomplishing a successful thoracoplasty. This latter consideration still influences many of our patients in favor of extrapleural pneumothorax. The remainder of the procedures in this particular classification were performed chiefly in females because of cosmetic considerations.

Combined Immediate Postoperative Results of all Extrapleural Procedures (Table IV): In all of the 148 procedures there were only 3 operative deaths or a mortality rate of 2 per cent. Two of these deaths occurred in hopeless cases while the third was the result of an immediate postoperative accident. The immediate operative results were highly successful in 129 instances or 87.2 per cent while the operation was a failure in 16 instances or 10.8 per cent of the total. As a result of our added experiences with this procedure, the incidence of operative failure has been reduced to a negligible minimum in recent years. Most of the failures occurred early in the series when we were not able to recognize the unfavorable cases prior to surgery. Aside from other more general considerations, we consider very dense disease, pachypleuritis, and large subpleural cavitation as definite contraindica-

TABLE IV

Combined Immediate Postoperative Results of all Extrapleural Procedures

Classification	Group Followed	Group Not Followed	Total	Per Cent
Successful	95	34	129	87.2
Operative Failure	8	8	16	10.8
Operative Death	1	2	3	2.0
Total	104	44	148	100.0

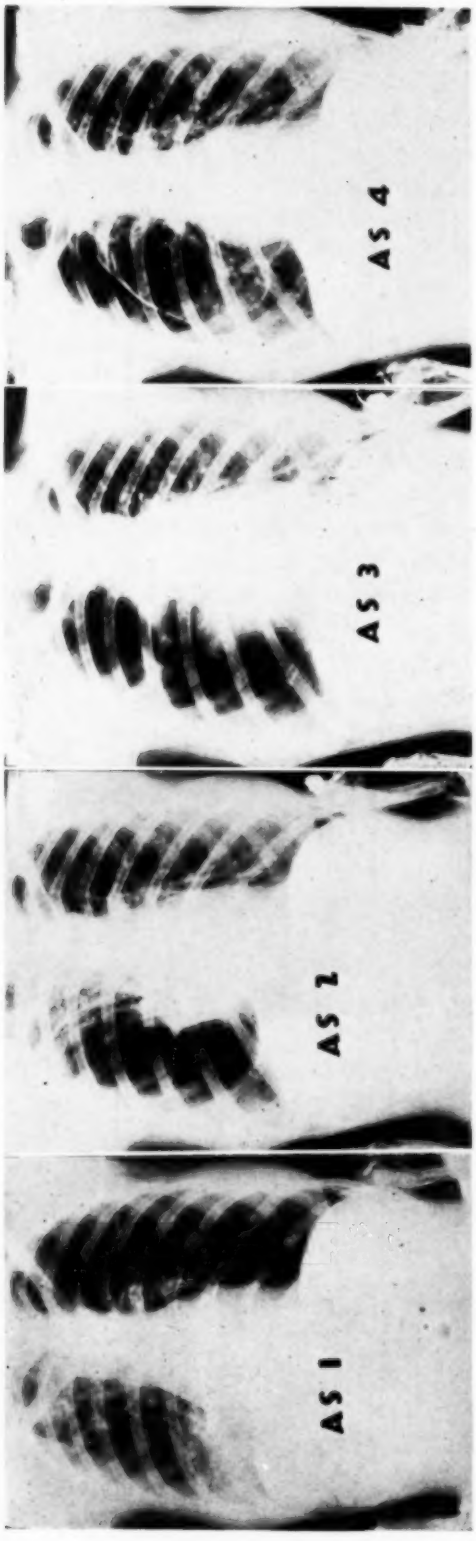

FIGURE 6: A. S., a 28-year-old white female. Very extensive disease on the right side (1). Intrapleural pneumothorax failed to control apical disease (2). Combined intrapleural and extrapleural pneumothorax established 4-4-40 (3). Eighty-six months later patient's disease is arrested (4). Has since given birth to healthy child and does all her own housework.

tions to extrapleural pneumothorax since they predispose to serious operative and postoperative complications (figures 8 and 9).

*Analysis of Long Term Results in 88 Patients Followed** (Table V): This particular analysis is confined to the 88 patients in whom the 95 immediate operative and postoperative results were successful (Table IV). These cases were observed for periods of time ranging from 12 months in some instances to almost 8 years in others. For expediency and simplification the long term results in these 88 patients have been arbitrarily classified as good, fair and poor. Sputum conversion, retrogression of the pulmonary disease and improvement in the patient's general condition are the criteria for a good result. On this basis 43.3 per cent of the hopeless patients and 64.6 per cent of all the remaining cases obtained good results. If the pulmonary disease remains stationary after operation with or without sputum conversion or general improvement, the result was considered fair. Ten per cent of the hopeless cases and 8.5 per cent of the remaining patients had only fair results by these standards. The result was considered poor if the pulmonary lesion showed signs of progression following surgery or if the patient's general condition continued to deteriorate. Poor results were obtained in only 6.7 per cent of the hopeless cases as compared to 11.9 per cent of all the remaining cases. The apparent discrepancy in favor of the hopeless group is nullified when one considers the fact that 40 per cent of the hopeless patients died during the period of observation as compared to only 15 per cent fatalities in all other cases followed. The important observation in this particular analysis, however, is the fact that 18 patients representing 60 per cent of the hopeless group followed are still alive today and more than 70 per cent of

*Does not include 8 operative failures and 1 operative death.

TABLE V

*Analysis of Long Term Results in 88 Patients Followed**

Results	Hopeless Cases		All Other Cases		Total Cases	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Good	13	43.3	38	64.8	51	58.0
Fair	3	10.0	5	8.5	8	9.0
Poor	2	6.7	7	11.9	9	10.2
Total Living	18	60.0	50	85.0	68	77.2
Total Dead	12	40.0	8	15.0	20	22.8
Total	30	100.0	58	100.0	88	100.0

*Does not include 8 operative failures and 1 operative death.

FIGURE 7: H. T., a 45-year-old white female. Far advanced disease and hopeless general condition. Right and left intrapleural pneumothorax failed (1). First stage extrapleural pneumothorax performed 4-11-41 (2). Disease subsequently spread to right base and continued to spread in left side (3). Condition unfavorable for thoracoplasty. Second stage extrapleural pneumothorax on 1-2-42 (4). Two years later the right side was making satisfactory progress, but hemorrhage from left lung was fatal (5).

these show signs of continued improvement and possible eventual arrest of the disease. If left on their own resources, there would unquestionably have been more than 12 deaths in the hopeless group at the time of this survey. Furthermore, 50 or 85 per cent of the group not classified as hopeless are alive today. Of these, 38 or more than 75 per cent show definite signs of continued improvement and hope for eventual arrest of the disease. The results of extrapleural pneumothorax therapy in this latter group compare most favorably with the results achieved by other more acceptable and widely-practiced measures of collapse therapy. Since 1944 there has not been a single death in the combined groups. During this time 23 operations were performed. Most of the fatalities prior to 1944 occurred during 1940 and 1941. These deaths were predominantly in the hopeless group and were more than likely the results of our own inexperience or unwise selection of the early cases in this series for surgery (figures 8 and 9).

All Complications Encountered in 104 Extrapleural Procedures (Table VI): Postoperative, sero-sanguinous fluid of varying amounts occurred in 100 per cent of the cases (figures 2, 4 and 5). It was usually harmless and with proper management was completely resorbed within one month following surgery. In a few instances, the fluid persisted for longer periods of time and some of these cases subsequently developed empyema. Emphysema was

TABLE VI

All Complications Encountered in 104 Extrapleural Procedures

Type	Number	Per Cent
Postoperative fluid	104	100.0
Emphysema	4	3.8
Empyema	13	12.5
Bronchopleural fistula	5	4.8
Lipoid pneumonia	1	0.9
External fistula	4	3.8

TABLE VII

Analysis of Empyema and Bronchopleural Fistula Cases

Method of Maintaining Collapse	EMPYEMA CASES		BRONCHOPLEURAL FISTULA CASES	
	No.	Per Cent	No.	Per Cent
Air (75 per cent)	8	61.6	1	20
Oil (25 per cent)	5	38.4	4	80
Total	13	100.0	5	100

an unimportant complication in 4 instances following surgery and required no special treatment (figure 5). Perfection of the operative technique has almost eliminated this minor and transient complication in recent years. Empyema, however, is by far the most important complication (figures 8 and 9). It occurred in 13 or 12.5 per cent of the cases. In 9 instances it was associated with 2 other serious complications, bronchopleural or external fistulae. The long term results in those patients who developed empyema or any of the other serious complications were, with few exceptions, uniformly poor. One patient accidentally developed a lipoid pneumonia following an unsuccessful attempt to fill the extrapleural space with oil. After a stormy course, this patient subsequently made an uneventful recovery from this complication.

Analysis of Empyema and Bronchopleural Fistula Cases (Table VII): In this series, approximately 75 per cent of the extrapleural spaces were maintained with air while, at one time or another, about 25 per cent were maintained with oil. Of the 13 instances of empyema, 61.6 per cent occurred in the group maintained with air while 38.4 per cent occurred in the group maintained with oil. Bronchopleural fistula occurred in only one case maintained with air while it was a complication in 4 cases maintained with oil. Although this is an admittedly limited study from which to draw any rigid conclusions, one is nevertheless impressed by the greater frequency of empyema and bronchopleural fistula as

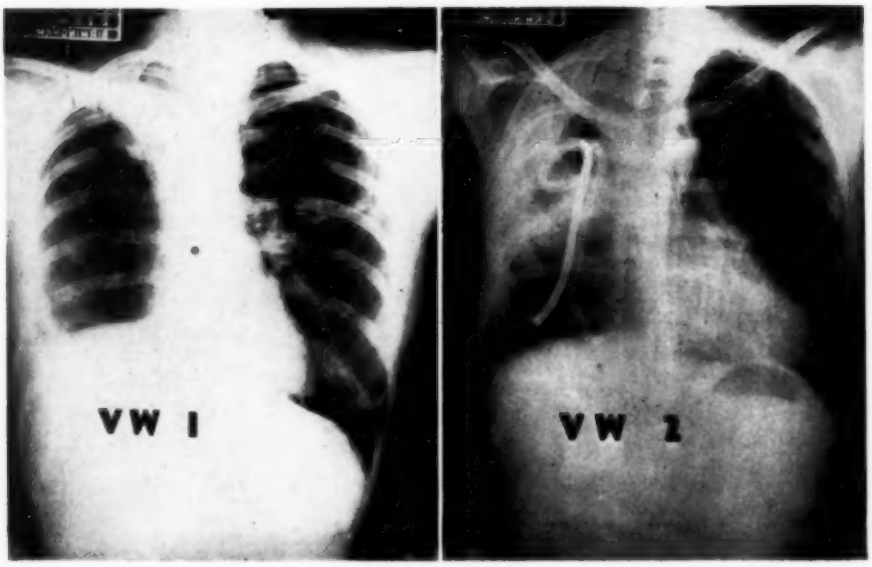

FIGURE 8: V. W., a 32-year-old white female. Very dense apical disease and pachypleuritis. Intrapleural pneumothorax failed (1). Following surgery he developed purulent empyema which required a thoracotomy (2). Patient is alive today following thoracoplasty.

complications in the group maintained with oil. As a result of these findings, we reserve extrapleural oleothorax for very special and rare occasions and avoid its use whenever possible.

Discussion: After careful evaluation of the statistical results obtained in this series of patients, we are satisfied to conclude that extrapleural pneumothorax is a very valuable form of temporary collapse therapy in the treatment of pulmonary tuberculosis. In fact, the results by comparison are as good, or better, than those obtained with other more generally practiced forms of collapse therapy. Our conclusion is, nevertheless, not in agreement with the majority of opinions expressed in the recent American literature. Perhaps the almost uniformly poor results reported by these investigators following their use of extrapleural pneumothorax reflects their inexperience with this particular type of procedure and poor choice of patients rather than a condemnation of this particular form of therapy. An unbiased evaluation of our earlier results clearly demonstrates and supports the latter observation. As our selection of patients, surgical technique and proficiency in the satisfactory maintenance of extrapleural space improved, so did our results. In many of these reports this procedure was used as a last resort in only hopeless cases when all other forms of therapy had failed or were not practicable. How, therefore, is it possible to equitably evaluate their results obtained with extrapleural pneumothorax on the same basis as the results

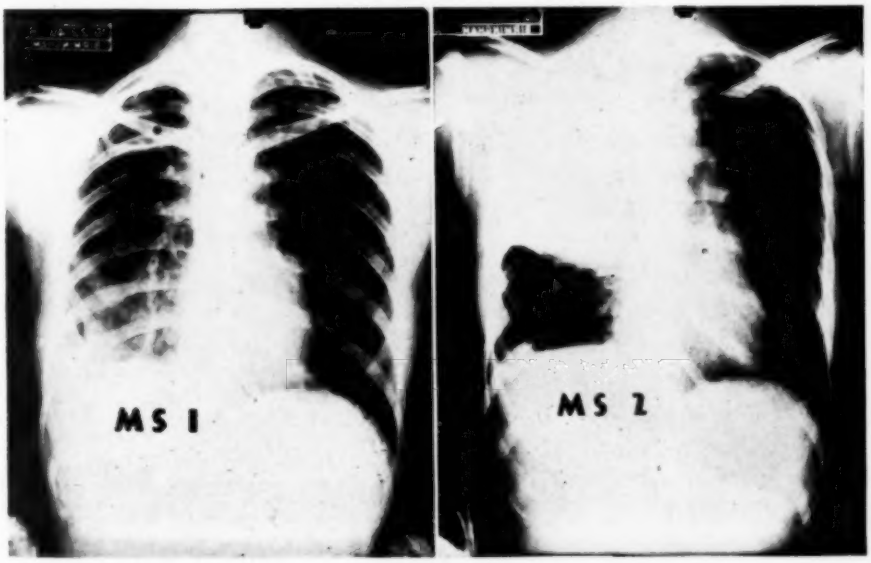

FIGURE 9: M. S., a 31-year-old white female. Unsuccessful intrapleural pneumothorax and large subpleural cavity on right side (1). During Surgery (6-40), accidental communication between extrapleural and intrapleural space established. Developed a purulent empyema and died 10 monthe later (2).

obtained with other forms of collapse therapy which usually were tried earlier and in more favorable cases.

It is true that in many cases the maintenance of a therapeutic extrapleural collapse is much more difficult and requires more painstaking effort than that involved in intrapleural pneumothorax therapy. The beneficial results which one can expect from a satisfactory extrapleural collapse more than justify this effort. A relatively larger number of the failures, poor results, serious complications and deaths recorded in this survey occurred in those patients whose follow-up treatment was entrusted to less experienced hands after discharge from the sanatorium. As a result of our unfortunate experience with extrapleural oleothorax (Table VII), we are not in a position to recommend its routine use as a solution to the difficult problem of maintaining an effective extrapleural space in the postsanatorium period of treatment. On the other hand, these disadvantages have been overcome to a large degree by treating out-patients ourselves or by teaching physicians in outlying districts how to administer air refills at proper intervals under our close supervision. In this connection, one may recall similar difficulties encountered in patients treated with intrapleural pneumothorax. On a comparative basis, the relatively simple surgical procedure involved in the production of an extrapleural space is not nearly as important in the ultimate prognosis as intelligent follow-up treatment. After the extrapleural space is established at surgery, its careful development and maintenance in the immediate postoperative period is an essential prerequisite for the ultimate success of the procedure. Spontaneous reexpansion is no more frequent than in an intrapleural pneumothorax if the case is followed and managed properly. Reexpansion, when indicated, is generally accomplished with ease and rapidity, although usually accompanied by a very dense pleural reaction (figure 5).

The selective nature of the collapse and absolute lack of surgical shock makes extrapleural pneumothorax the collapse procedure of choice for patients in the older age group and for those in poor general condition. Its interference with physiologic pulmonary function is minimal and much less than all other methods of collapse therapy. Therefore, it can be utilized in those patients who already have impaired pulmonary function as evidenced by a lowered vital capacity. Similarly, it can be used as a temporizing measure when the occasion warrants in preparation for a future thoracoplasty on the ipsolateral or contralateral side. In the presence of scattered apical disease we feel that an extrapleural pneumothorax is actually preferable to thoracoplasty provided there is no cavity larger than 4.5 cm. and that total cavitation

is not excessive. The so-called hilar cavity is frequently benefited by this form of therapy since it is more accessible to direct collapse. We also reserve this procedure for those patients who refuse to submit to thoracoplasty either because of fear or cosmetic considerations. Although the latter utilization of extrapleural pneumothorax has no valid medical basis, nevertheless, it is better than no treatment at all in the uncooperative patients. We, further, are of the opinion that extrapleural pneumothorax is especially designed for communities with limited sanatorium facilities. It can be accomplished without undue danger to the patient in the presence of limited surgical and nursing facilities since it is a much simpler and less shocking procedure than thoracoplasty. In addition, the period of convalescence and rehabilitation of the patient is generally more rapid.

The foregoing comments clearly indicate our position in regard to extrapleural pneumothorax as a form of temporary collapse therapy in pulmonary tuberculosis. We wish to emphasize, however, that this form of therapy is not offered as a panacea or substitute for all other forms of collapse therapy but rather as an acceptable and valuable additional therapeutic measure to supplement the phthisiologist's manifestly inadequate and unsatisfactory armamentarium.

SUMMARY

1) A statistical analysis of the results achieved with extrapleural pneumothorax over an eight year period has been presented and discussed.

2) After careful evaluation of this survey of our experiences, we are satisfied to conclude that extrapleural pneumothorax is a very valuable form of temporary collapse therapy in the treatment of pulmonary tuberculosis.

RESUMEN

1) Se presenta y discute un análisis estadístico de los resultados obtenidos en un período de ocho años con el neumotórax extrapleural.

2) Después de avaluar cuidadosamente nuestra experiencia, estamos satisfechos de que podemos sacar la conclusión de que el neumotórax extrapleural es una forma muy valiosa de la colapsoterapia temporaria en el tratamiento de la tuberculosis pulmonar.

REFERENCES

1 Binney, H.: "Extrapleural Pneumothorax," *Ann. of Surg.*, 110:578, 1939.
2 Tuffier, T. (quoted by Russo, J. G.): "Extrapleural Pneumothorax," *J. of Thoracic Surg.*, 12:316, 1943.

Discussion

PAPKEN S. MUGRDITCHIAN, M.D., F.C.C.P.
Beirut, Lebanon

We have operated on 17 patients (one had bilateral operation). Eight of these were done in 1938-41; 9 in 1945-46. In the first group 3 had empyema, 6 eventually died, 2 are living and well, one of which had good air refills for four years and the lung reexpanded subsequently without difficulty. Of the 9 in the second group, 2 had contralateral thoracoplasty. One developed an empyema necessitans that is clearing. In 7 patients the air was replaced with gomenol oil. All cavities remain apparently closed, the sputum was converted in 8 cases and to date there has been no mortality.

Although the numbers are small and the second group only one year old, it is interesting to note the strikingly different results obtained in the two groups. The same technique was used in both groups. This illustrates the varied results reported by different clinics on the same operative procedures. The range of indications appear to be the determining factor. As with most new operations there has been a tendency to try the bad cases first; naturally results are also bad. In the first group nearly all were hopeless bilateral cases, while the second group did not include the more widespread subacutely progressive cases. Here some antibiotics may be used advantageously in an attempt to stabilize the lesions prior to other anticipated operative interferences. The majority of the patients in the second group had bilateral cavities; few others, especially women, refused thoracoplasty.

The late progressive loss of the extrapleural pocket and the incidence of empyema seem to be reduced when: 1) Bleeding is carefully controlled at operation, blood clots are removed even by open approach if necessary. 2) Pre and postoperative use of antibiotics such as penicillin. (Streptomycin should prevent most of the tuberculous empyemas). 3) The extrapleural pocket is blocked early by oil (4-6 weeks postoperative), at a time when the size of the pocket seems to be optimal. Oil pressure readings are taken at regular intervals. Results seem to be encouraging. We intend to try more cases and over longer periods of observation.

An extrapleural pneumonolysis with contralateral thoracoplasty is preferred to bilateral thoracoplasty; respiratory function is less disturbed. At first the extrapleural is done on the more recent and less extensive side. Later the thoracoplasty is done on the other side the size being accommodated to the extent and position of the lesions, and the respiratory reserves of the patient.

Relationship of the Pleural Fluid Sugar to Pulmonary Tuberculosis

STEPHEN M. GELENGER, M.D., F.C.C.P.
and RUSSELL F. WIGGERS, M.D.
Flint, Michigan

Because of the characteristic low sugar content of the spinal fluid in cases of tuberculous meningitis, it was decided to study this phenomena in pleural effusions, in an effort to determine the relationship, if any, of tuberculous pleural effusion and the pleural fluid sugar.

Up to the present time the only work reported along this line was that of E. Nassau. He found that those cases of exudative pleurisy with a positive tubercle bacillus culture had a sugar content between 15 and 84 mgs. per cent, with an average of 49.25 mgs. per cent, as compared with a range of 80 to 132 mgs. per cent. and an average of 115.16 mgs. per cent in the negative bacilli cases. He further discovered that in pneumothorax pleurisy the sugar ranged from 63 to 136 mgs. per cent, with an average of 88.5 mgs. per cent in the negative bacilli cases, whereas in the tubercle bacillus positive cases the sugar determination fell between 4 and 92 mgs. per cent, averaging 44.46 mgs. per cent. In tuberculous empyema the sugar varied from 7 to 22 mgs. per cent, with the average at 12.4 mgs. per cent.

Procedure

A total of 33 cases of pleural effusion comprises the series. Comprehensive histories were taken and complete physical examinations were given each patient. Routine blood and urine studies as well as chest x-ray films were made. In cases where indicated, other procedures such as biopsy, sputum and bronchoscopic examinations were done.

The fluid removed from the chest was subjected to the following tests: specific gravity, total protein, cell count, total sugar, stained smear, culture, and guinea pig inoculation. A venous blood sugar was drawn at the same time for comparison with the pleural fluid sugar.

Many of the cases required repeated examinations of the pleural fluid in order to establish the diagnosis. However, for purposes of standardization only the original sugar determination was used.

Sugar determinations on the subsequent thoracenteses tended to approximate closely the original determination.

Sugar determinations were made by the Folin-Wu method using a photo-electric colorimeter. The pleural fluid was concentrated by Petrof's method and cultured on Petragnani's medium and inoculated into the inguinal lymph nodes of two guinea pigs which were autopsied at three and eight weeks respectively.

We were able to establish the etiology of 31 of the 33 cases. The remaining two cases failed to reveal the cause of the effusion after an extensive search.

RESULTS

GROUP 1 — 8 CASES:	
Tuberculosis	8
GROUP 2 — 4 CASES:	
Tuberculosis	2
Bronchogenic carcinoma	1
Unknown	1
GROUP 3 — 21 CASES:	
Post pneumonic	9
Primary bronchogenic carcinoma	3
Traumatic	2
Metastatic malignancy to lung	2
Carcinoma of stomach	1
Metastatic abscess to lung	1
Spontaneous pneumothorax	1
Congestive heart failure	1
Unknown	1

On the basis of the amount of sugar in the pleural fluid, all the cases could be divided into three general groups.

Group 1: Those with a pleural fluid sugar below 30 mgs. per cent.

Group 2: Those with a pleural fluid sugar between 30 and 60 mgs. per cent.

Group 3: Those with a pleural fluid sugar above 60 mgs. per cent.

There were eight cases in Group 1 where the sugar ranged from a trace to 25.1 mgs. per cent. The average of this group was 10.9 mgs. per cent. At the same time the venous blood sugars varied from 82 to 142 mgs. per cent. In every one of the eight cases tubercle bacilli were demonstrated either by culture or guinea pig inoculation of the pleural fluid. Many required repeated search for the organisms, which sooner or later were found. In none of these cases was there x-ray evidence of tuberculosis.

In Group 2 there were four cases. The pleural fluid sugars varied from 30.3 to 39.5 mgs. per cent, averaging 36.3 mgs. per cent. The venous blood ranged from 104 to 122 mgs. per cent. In two of the four cases tuberculosis was subsequently diagnosed. One patient

had a bronchogenic carcinoma, while the fourth failed to reveal the cause of the effusion. The latter has been followed for a period of two years without developing subsequent complications.

Group 3 consisted of 21 cases, all of which had a pleural fluid sugar between 62 and 140 mgs. per cent. Venous blood determinations fell between 79 and 166.7 mgs. per cent. Tuberculosis was not found to be present in any of this group. After appropriate study, the cause of the effusion was found in all except one case. The greatest majority were post-pneumonic in origin. There were nine such cases. The effusion accompanied primary carcinoma of the lung in three instances. Two were traumatic. Likewise, two resulted from metastatic growths in the lungs. There was one case each of congestive heart failure, carcinoma of the stomach, metastatic lung abscess, and spontaneous pneumothorax with pleural effusion. Repeated examinations of one patient failed to disclose the cause of the effusion. This case has been followed for six months, and up to the present time there have been no further developments.

Conclusions

We hesitate to draw specific conclusions from this small series of cases, but it seems very probable that the determination of the pleural fluid sugar may be quite useful diagnostically in the obscure sero-fibrinous pleural effusions.

The lower the sugar level the greater the possibility of tuberculosis. All of the cases of tuberculosis had a level below 39.5 mgs. per cent. The average sugar determination of all cases of tuberculosis was 15.7 mgs. per cent. A finding of 30 mgs. per cent or less should be considered diagnostic of tuberculosis and should be followed by an intensive search for the organism.

Cases with borderline values of pleural fluid sugar should be considered as tuberculous until proved otherwise.

If the sugar level is above 60 mgs. per cent it is quite unlikely that the cause of the effusion is tuberculosis.

SUMMARY

A series of 33 cases of pleural effusion were studied, as to the sugar determination of the pleural fluid. The sugar findings fell into three groups:

Group 1: those with a sugar determination below 30 mgs. per cent (8 cases). Group 2: those between 30 mgs. and 60 mgs. per cent (4 cases). Group 3: those above 60 mgs. per cent (21 cases).

All the Group 1 cases were found to have tuberculosis. Two of the Group 2 cases had tuberculosis. The rest had some other

pathology as the cause of the effusion. All of the tuberculous effusions had a sugar level of 39.5 mgs. per cent or below.

It was concluded that this determination might be an aid in the diagnosis of the obscure pleural effusions.

RESUMEN

Se estudió una serie de 33 casos de pleuresía con derrame mediante mediciones de la azúcar en el derrame pleural. Los hallazgos relativos a la azúcar se dividieron en tres grupos:

Grupo 1: aquellos con mediciones de azúcar de menos de 30 mgs. por ciento (8 casos). Grupo 2: los casos entre 30 mgs. y 60 mgs. por ciento (4 casos). Grupo 3: los casos con más de 60 mgs. por ciento (21 casos).

Se descubrió que todos los casos en Grupo 1 tenían tuberculosis. Dos de los casos en Grupo 2 tenían tuberculosis. En los otros el derrame se debía a otra causa. Todos los derrames tuberculosos tenían un nivel de azúcar de 39.5 mgs. por ciento o menos.

Se sacó la conclusión de que esta medición puede ser de ayuda en el diagnóstico de derrames pleurales de origen oscuro.

REFERENCE

1 Nassau, E.: "Diagnostic and Prognostic Value of Estimations of the Free Sugar in Pleural Effusions," *Tubercle,* 22:249, 1941.

Tuberculosis in Children*

SAMUEL L. PAINTER, M.D.
Cincinnati, Ohio

A review of 234 cases admitted to the Dunham Hospital between the years 1942-1947 inclusive.

There has been growing controversy in recent years as to the proper care of the child with a primary tuberculous infection. Some observers (Wallgren[1] and Pottenger[2]), feel that rest in bed is the indicated treatment during the active stage of the disease; whereas others (Myers[3] and Levine[4]), state that prolonged bed rest and hospitalization have no effect on the eventual outcome of a primary infection.

Because of the diverse opinions which still exist regarding the proper management of this disease, it was felt that a review of the cases admitted to this hospital might be of some value in attempting to decide this point.

There were 234 cases admitted to the Children's Ward between January 1, 1942 and December 31, 1947. The ages ranged from five months to thirteen years. The criteria for admission to the hospital were: (1) a positive reaction to the tuberculin test, and (2) x-ray evidence of an active pulmonary or tracheo-bronchial lymph node lesion. A definite history of contact was obtained in the majority of the patients admitted, but this was not considered an absolute criteria for admission. There were 118 white children, and 116 negroes, of which 122 were females, and 112 were males. The age incidence can be seen in table 1.

Of the 234 cases admitted in this six year period, 186 (79.5 per cent), were diagnosed on admission as having primary tuberculosis. The admission diagnoses of the remaining forty-eight cases (20.5 per cent) can be seen in table 2. Five children (2.0 per cent) were diagnosed as non-tuberculous after admission to the hospital.

There were twelve deaths (5.1 per cent) in this six year period. Nine of these deaths were ascribed to miliary tuberculosis with or without meningitis. Eight of these patients had miliary tuberculosis at the time of admission, while one patient was admitted with a diagnosis of an active primary infection, and two weeks after admission to the hospital, he became acutely ill and died on the sixty-ninth hospital day of miliary tuberculosis with meningitis. One seven month old white male died of far advanced pulmonary

*Presented at the Annual Meeting, Ohio Chapter, American College of Chest Physicians, March 30, 1948, Cincinnati, Ohio.

tuberculosis with cavitation. One death was attributed to sickel-cell anemia, and one patient died of transverse myelitis of undetermined etiology.

All of the patients admitted were evaluated on the basis of the following criteria:

1) History of contact.
2) Reaction to the tuberculin test (intra-dermal).
3) Clinical symptoms on admission (asymptomatic, chronically ill, or acutely ill).
4) Temperature on admission.
5) Examination of the gastric washings for the presence of acid-fast bacilli. (This includes smear, culture, and guinea pig inoculation).
6) The development of tuberculous complications after admission to the hospital.
7) Re-admissions to the hospital with tuberculous complications.

The results of this study are given in table 3.

As demonstrated in table 3, out of the 186 children admitted with a diagnosis of a primary infection, 167 (89.8 per cent) were asymptomatic, and 166 (89.3 per cent) were afebrile on admission to the hospital. Seventeen children (9.1 per cent) were considered chronically ill on admission. Eight of the chronically ill patients had a serious nontuberculous complication at the time of admission which was contributing to their illnesses. Two patients (1.1 per cent) were admitted acutely ill; one had acute tonsillitis which

TABLE I

Age in Years	Under 1	1	2	3	4	5	6
No. of Cases	15	19	27	23	26	21	12
Age in Years	7	8	9	10	11	12	13
No. of Cases	26	23	11	10	10	17	4

TABLE 2

	No. of Cases	Per cent
Primary tuberculosis	186	79.5
Pleurisy with effusion	21	9.0
Miliary tuberculosis	14	6.0
Re-infection tuberculosis (Adult Type)	7	3.0
Non-tuberculous	5	2.0
Tuberculous meningitis (with no demonstrable pulmonary lesion)	1	0.5
TOTAL	234	100.0

responded promptly to sulfadiazine therapy, the other had sickle-cell anemia in a hemolytic crisis. Twenty patients (10.7 per cent) were febrile on admission, five of whom presented no other signs or symptoms of illness other than temperature elevation.

Acid-fast bacilli were demonstrated in thirty-eight patients (20.4 per cent) of the group admitted with primary tuberculosis. Thirty-four of these were positive on guinea pig inoculation only and four were positive on culture as well as guinea pig inoculation. Prior to January 1, 1946, each guinea pig was inoculated with one gastric washing. Twelve of the thirty-eight positive results were obtained prior to 1946. However, starting in January 1946, each guinea pig was inoculated with three gastric washings and twenty-six positives were reported in two years as compared with twelve positives in four years prior to January 1946.

Six patients (3.3 per cent) developed tuberculous complications after admission to the hospital, out of the group admitted with a primary infection. Of these, three patients developed pleurisy with effusion, and there was one case each of miliary tuberculosis, tuberculosis of the spine, and a post-primary spread of the infection. Abstracts of these cases are presented below.

Case 1: A five year old colored male was admitted to the hospital in March 1942. He had a definite history of contact and a positive reaction to the tuberculin test. He was afebrile and asymptomatic on admission. Physical examination revealed no abnormal findings and chest x-ray film showed a primary infection. Gastric washings were negative for acid-fast bacilli. The patient developed acute tonsillitis after four weeks in the hospital, and this was followed by pleurisy with effusion on the left. The patient recovered with no further complications, and was discharged after 620 days in the hospital.

Case 2: A nine year old colored female was admitted in June 1942. There was a definite history of contact, and the tuberculin test was positive. The patient was chronically ill, and ran a persistent low grade fever. Physical examination was non-contributory except for moderate malnutrition. Chest x-ray film on admission was interpreted as a retrogressive primary infection. The patient, however, did not respond well to routine care, and developed pleurisy with effusion after several months of hospitalization. This ultimately cleared, and she was discharged after 747 days in the hospital.

She was not seen again until June 1945, when at the age of twelve years she was admitted with a diagnosis of moderately advanced pulmonary tuberculosis. The patient again was chronically ill, and ran persistent low grade fever. Gastric washings were positive for acid-fast bacilli on guinea pig inoculation. The lesion responded well to bed rest, and the patient was discharged on the 235th hospital day.

Her final admission was in August 1946. At this time the patient was acutely and seriously ill, with a spiking fever to 106 degrees F. Admission chest x-ray film revealed hematogenous dissemination of the disease, and the patient died on the forty-seventh hospital day of tuberculous meningitis.

TABLE 3

Admission Diagnosis	Number of Cases	History of Contact	Asymptomatic	Chronically Ill	Acutely Ill	Afebrile	Febrile	Positive Tuberculin Test	Gastric Washings Positive for Acid-fast	Tuberculous Complication after admission	Non-tuberculous Complications	Re-Admissions with Tuberculous Complications	Deaths
Primary Tuberculous Infection	186	138	167	17	2	166	20	165	38	6	23	3	2
Pleurisy with Effusion	21	11	15	5	1	18	3	20	8	0	2	0	1
Miliary Tuberculosis	14	7	7	1	6	6	8	9	5	5	2	0	7
Re-infection Tuberculosis	7	6	2	3	2	3	4	6	6	2	1	1	1
Non-tuberculous	5	2	3	1	1	2	3	0	0	0	0	0	0
Tuberculous Meningitis	1	1	0	0	1	0	1	1	0	0	0	0	1
TOTAL	234	165	194	27	13	195	39	201	57	13	28	4	12

Case 3: A six year old colored girl was admitted in May 1942. The tuberculin test was positive and a definite history of contact was obtained. The patient was afebrile and symptom free on admission, and physical examination revealed no abnormal findings. Chest x-ray film revealed an active primary infection. Tubercle bacilli were demonstrated on guinea pig inoculation. Shortly after admission the patient became acutely ill, and a repeat chest x-ray examination showed a miliary dissemination of the disease and the patient developed signs and symptoms of meningitis. The patient died on the sixty-ninth hospital day of tuberculous meningitis.

Case 4: A seven year old colored male was admitted in July 1943 with a history of contact. The tuberculin test was positive. The patient ran a persistent low grade fever, but otherwise did not appear ill. Admission chest x-ray film revealed an active primary infection. Physical examination revealed no abnormal findings. Gastric washings were positive for acid-fast bacilli on guinea pig inoculation. The patient developed right pleurisy with effusion four weeks after admission. This gradually cleared without further complications and the patient was discharged after 338 days in the hospital.

Case 5: A five year old colored boy was admitted in April 1943 with sickle-cell anemia and primary tuberculosis. He had a definite history of contact, and the tuberculin test was positive. The patient was acutely ill on admission and ran a persistent spiking fever. He required frequent blood transfusions for his severe anemia. The patient ultimately developed tuberculosis of the spine. Gastric washings were negative for acid-fast bacilli. The patient died of sickle-cell anemia after 1,416 days in the hospital.

Case 6: An eighteen month old white male was admitted in August 1947. No history of contact was obtained, but the tuberculin test was positive. The patient was chronically ill, listless and ran a persistent fever as high as 102 degrees F. Admission chest x-ray film revealed an active primary infection, with a large patch of parenchymal infiltrate on the right. Although all signs and symptoms abated and the temperature returned to normal, a repeat chest x-ray examination showed a definite spread of the initial pulmonary lesion. Gastric washings were positive for acid-fast bacilli on guinea pig inoculation. Serial x-ray examinations showed gradual clearing of the pulmonary lesion without further complications.

Three patients (1.1 per cent) were re-admitted to the hospital for tuberculous complications which developed after discharge. One was the nine year old colored girl who ultimately died of tuberculous meningitis. The other two were children who were discharged with a diagnosis of a retro-gressive primary infection, both of whom were re-admitted within thirty days after discharge with pleurisy and effusion. Both patients recovered without further complications.

To summarize then, there were nine children (4.4 per cent) who developed tuberculous complications out of the group of 186 patients originally admitted with a diagnosis of primary tuber-

culosis. Six of these complications developed while the patients were still in the hospital, and three patients developed complications after medical discharge from the hospital which were severe enough to require re-admission. There was a definite history of contact in eight of the nine patients, and acid-fast bacilli were demonstrated in six out of the nine cases. The tuberculin test was positive in all nine patients. Six of the children were febrile or presented symptoms of illness on admission to the hospital, while three were entirely afebrile and symptom-free on admission.

There were twenty-eight children (11.9 per cent) who developed non-tuberculous complications after admission to the hospital. Twenty-six of these were acute contagious diseases, there was one patient who developed a non-specific corneal ulcer, and one patient fractured his arm falling out of bed.

The hospital stay in days for children with a primary infection ranged from a minimum of twelve days to a maximum of 1,416 days, with an average of 250 days per patient. Treatment on the childrens ward consists of general supportive care. The children are kept in bed at all times. When they become too active in the judgment of the nurses on the floor, restraining jackets are used. Those children who are of school age go to and from the classroom on the ward in a wheel-chair, and attend classes for one hour daily. All of the children take a two and a half hour nap daily. They receive a 2000-2200 calorie diet and are given cod-liver oil and Feosol daily. None of the patients with a primary infection have received specific therapy in any form. Streptomycin has not been used at this hospital for the treatment of primary tuberculosis. Serial chest x-rays are taken every two months routinely. Children are usually not considered ready for discharge until there has taken place complete absorption of the parenchymal lesion, and contraction or calcification in the regional lymph nodes. All cases for discharge are presented before the entire hospital saff in a manner similar to the routine with adult patients.

Comment

From this study, it is evident that the overwhelming majority of children with a primary infection do well with no specific therapy. The trend in recent years has definitely been away from the special care which these patients formerly received. In the final analysis, hospitalization of these patients offers just one advantage, and that is the opportunity to diagnose a tuberculous complication in its early stages. With the clinic care which is now available, this responsibility could be taken over by the clinics. Then too, the emotional stress which is placed both upon the

parents and the child by long term hospitalization is sufficient in itself to contra-indicate this type of care unless absolutely necessary.

A more critical evaluation of patients with a primary infection seems indicated with respect to long term hospitalization. Assuming that only those children with a positive tuberculin test and chest x-ray evidence of an active primary infection would be candidates for hospitalization, admissions should be limited to those patients who satisfy the following criteria.

1) A definite history of contact, preferably in the immediate family group, where the exposure is intimate.
2) The presence of acid-fast bacilli in the gastric washings on repeated examinations at monthly intervals.
3) Clinical symptoms of illness and fever.
4) Definite progression of the pulmonary lesion on chest x-ray examination.
5) The development of tuberculous complications, either pulmonary or extrapulmonary.

SUMMARY

1) There were 234 patients admitted to the hospital between January 1, 1942, and December 31, 1947. There was no significant variation in the age, race, or sex of the patients admitted.

2) One hundred and eighty-six (79.5 per cent) of the patients were diagnosed on admission as having primary tuberculosis. Of this group, 167 (89.8 per cent) were asymptomatic, and 166 (89.3 per cent) were afebrile on admission. Acid-fast bacilli were demonstrated in 38 patients (20.4 per cent).

3) Six children (3.3 per cent) admitted with a primary infection developed tuberculous complications after admission to the hospital. Three children (1.1 per cent) required readmission to the hospital, after medical discharge for tuberculous complications. Eight of these patients had a definite history of contact, and tubercle bacilli were demonstrated in six of these patients. Six children had clinical symptoms of illness or fever, while three were afebrile and asymptomatic, prior to the development of their tuberculous complications.

4) Treatment consisted of bed rest and an adequate diet. No specific therapy was instituted in any case with a primary infection. The average hospital stay for patients with a primary infection was 250 days.

RESUMEN

1) Se admitieron a 234 pacientes al hospital desde el 1o. de enero de 1942 al 31 de diciembre de 1947. No hubo variación significativa en la edad, raza o sexo de los pacientes admitidos.

2) Se hizo el diagnóstico de tuberculosis primaria en 186 (79.5 por ciento) de los pacientes admitidos. De este grupo, 167 (89.8 por ciento) eran asintomáticos y 166 (89.3 por ciento) no tenían fiebre cuando fueron admitidos. Se demostraron bacilos ácido-rresistentes en 38 pacientes (20.4 por ciento).

3) Seis niños (3.3 por ciento) admitidos con una infección primaria desarrollaron complicaciones tuberculosas después de haber sido admitidos al hospital. Tres niños (1.1 por ciento) necesitaron readmisión al hospital debido a complicaciones tuberculosas después de haber sido dados de alto. Ocho de esos pacientes presentaron una historia de contacto bien definido y se demostraron bacilos tuberculosos en seis de ellos. Seis niños tenían signos clínicos de enfermedad o fiebre, mientras que tres no tenían fiebre u otro síntoma, con anterioridad al desarrollo de las complicaciones tuberculosas.

4) El tratamiento consistió de reposo en cama y dieta adecuada. No se empleó terapia específica en ningún caso de infección primaria. El promedio de la estadía en el hospital de los pacientes con la infección primaria fue 250 días.

REFERENCES

1 Wallgren, A.: "Tuberculosis in Children," *Nelson Loose-Leaf Medicine*, Chapter 13A, p. 396. Thomas Nelson and Sons, New York.

2 Pottengen, F. M.: "Tuberculosis," p. 153, *C. V. Mosby Co.*, St. Louis, 1948.

3 Myers, J. A.: "Tuberculosis in Children and Young Adults," p. 169, *Charles Thomas*, Springfield, Illinois, 1938.

4 Levine, M.: "Primary Tuberculosis, Effect of Unrestricted Activity on Prognosis," *Am. J. Dis. Child.*, 68:385, 1944.

Pathologic Aspects of Atypical Pneumonias
(Interstitial Pneumonitis)

W. A. D. ANDERSON, M.A., M.D., F.A.C.P.*
Milwaukee, Wisconsin

In this discussion of interstitial pneumonitis, (or interstitial pneumonia, atypical pneumonia), it is intended to present certain aspects of the underlying pathologic changes in both common and unusual types of atypical pneumonias. Very many and very diverse injurious agents can and do injure the tissues of the lung and cause inflammatory reaction and disease. The lung tissues, however, have a limited reactive capacity, or a limited number of ways in which they can react to the diverse injurious agents. The pneumonias produced are anatomically classified as lobar, lobular or broncho—, and interstitial (commonly called interstitial pneumonia or interstitial pneumonitis).

Interstitial pneumonitis is characterized by the fact that in inflammatory reaction and inflammatory exudate is found predominantly in the interstitial tissues, the supporting framework of the lung (in bronchioles, peribronchiolar tissues, and alveolar walls), rather than in alveolar spaces. Also, characteristically, the cells of the inflammatory exudate tend to be predominantly of mononuclear types, rather than neutrophilic polymorphonuclear leucocytes. In certain varieties of interstitial pneumonia, the epithelial lining cells of bronchioles and of alveoli show peculiar changes. Sometimes interstitial pneumonitis is accompanied or followed by a progressive fibrosis.

In general, one can say that this interstitial type of pulmonary change most often is a reaction to injury by microorganisms which live and grow only within living cells—viruses, rickettsiae, certain protozoa, such as toxoplasma, and certain types of fungi, such as histoplasma. The higher bacteria, which are capable of growth without the enzyme systems found in living cells, only uncommonly cause this type of reaction. One could speculate with considerable interest about reasons why microorganisms which prefer to be or are obliged to be intracellular in their parasitism, elicit a certain type of response on the part of the pulmonary tissues.

---

*From the Department of Pathology and Bacteriology, Marquette University School of Medicine, Milwaukee, Wisconsin. Presented at the Third Annual Meeting of the Wisconsin Chapter, American College of Chest Physicians, Milwaukee, Wisconsin, October 5, 1947.

Influenzal Pneumonia

Studies of the pandemic of influenza during and after World War I, indicated that in cases in which death occurred during the first five days of illness, the pulmonary lesions were an interstitial pneumonitis similar to that found in the current atypical pneumonia. When the clinical duration was greater than one week, secondary bacterial infection with streptococci, pneumococci or other organisms was the rule, and some variety of a bronchopneumonia or lobar pneumonia resulted. These studies, and also experimental studies on influenza in swine, lead to the conclusion that influenza, uncomplicated by secondary bacterial infection, is characterized by a pulmonary lesion of acute interstitial pneumonitis.[1,2]

Acute Interstitial Pneumonitis, Etiology Undetermined (Atypical Pneumonia)

Most details about the atypical pneumonia which has been prevalent now for almost a decade are quite familiar. The etiology, although presumably viral, still lacks complete proof. The mortality in uncomplicated cases has been very low, so that few pathologists have had an opportunity to study more than a few isolated cases. Reimann,[5] in a review published in May 1947, stated that only about 20 necropsy reports were available and that many of these were incomplete. However, the unparalleled opportunity provided by the central pathologic laboratory of the United States army, made more than 42 cases available in one series.[3] Parker, Joliffe and Maxwell[16] have recently reported on eight necropsied cases. From published reports and personal experience a composite description of the pulmonary lesion may be given.

The lungs are slightly or moderately increased in weight. The pleural surfaces are usually smooth and glistening, but occassionally there are patches of fibrinous pleurisy. Pleural effusion is unusual. The extent of lung involvement varies from a portion of a lobe, to a whole lobe, a whole lung, or a diffuse bilateral spread. Focal, slightly-raised, whitish areas on the cut surface are involved bronchioles, which contain a thick mucopurulent material. Surrounding tissue is congested, and sometimes edematous or hemorrhagic.

Microscopic sections of the larger and medium-sized branches of the bronchial tree show intact mucosa, with marked submucosal edema, congestion, and infiltration by mononuclear cells. Involved bronchioles, which have a spotty distribution, show characteristic changes. The lumens contain a mixture of pus,

desquamated mucosa, and mucoid fluid. The bronchiolar mucosa is ulcerated. The walls are thickened, often markedly, by an abundant exudate of plasma cells, lymphocytes, monocytes and edema fluid. Neutrophilic leucocytes are scanty. The affected bronchioles are often dilated, the fibers of their walls being degenerated or fragmented. The cellular and fluid exudate extends radially into peribronchial tissues and adjacent alveolar walls. Affected alveolar walls may be thickened to several times their normal dimensions, but are not ruptured or necrotic. The alveolar spaces may be air-containing, atelectatic, or may contain serous exudate with a few mononuclear cells. The serous exudate often is crowded to the periphery of the alveolar space, forming a hyaline membrane. Microorganisms may be demonstrable in bronchiolar lumens, but are absent elsewhere in the involved tissue.

Metaplasia of lining epithelial cells is quite a common finding. Bronchiolar lining cells may show a focal or more diffuse metaplasia to a squamous type, and alveoli also may show a lining of metaplastic epithelial cells of columnar type, or even squamous areas.

In some cases pleurisy may be present. A thin layer of fibrin without leucocytes is present on the surface. The subpleural tissues are edematous, congested, and infiltrated by monocytes, lymphocytes, and plasma cells.

Such is the basic picture of interstitial pneumonitis. The various conditions to be described are but variations of this picture in which certain features are prominent and others subdued. A number of conditions in which a viral origin has been more conclusively demonstrated give a similar or indistinguishable picture. Psittacosis and other forms of ornithosis are examples, although they are known to account for but a very small proportion of clinical cases of atypical pneumonia. Q fever, at one time thought to be due to a viral organism, but now usually classed as a rickettsia, also has a very similar clinical and pathologic picture.

Rickettsial Pneumonitis

Various rickettsial diseases may have, among other tissue involvements, an interstitial pneumonitis which in its essentials is the same as that of atypical pneumonia. This occurs almost invariably in Q fever, in about half the cases of tsutsugamushi disease (scrub typhus), and less frequently and with less severity in typhus fever and Rocky Mountain spotted fever.

The rickettsial interstitial pneumonitis, as exemplified by that seen in scrub typhus,[6] shows bronchiolar involvement, the lumens filled with purulent exudate mixed with mucous and desquam-

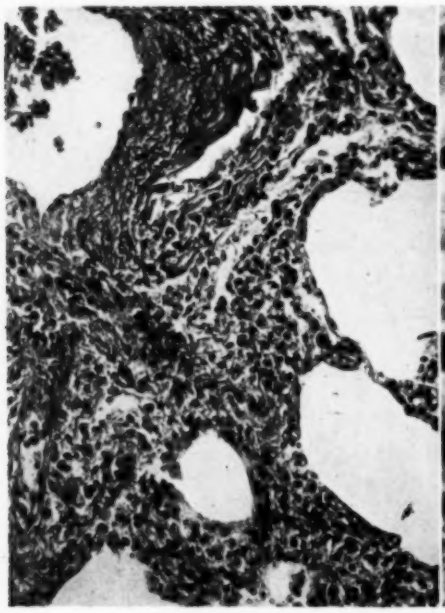

FIGURE 3

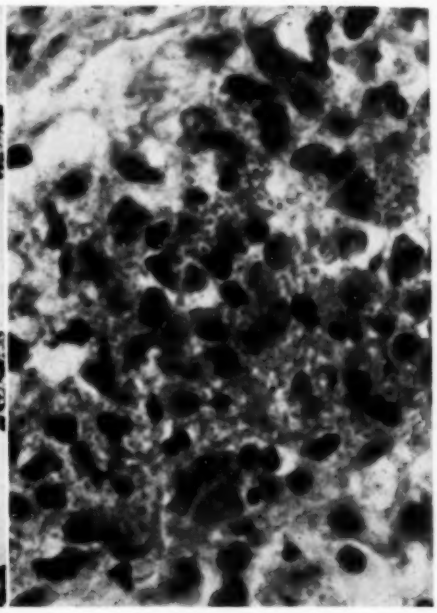

FIGURE 4

Figure 3: Pulmonary histoplasmosis, showing interstitial pneumonitis.—*Figure 4:* Pulmonary histoplasmosis, showing numerous encapsuled histoplasma within the cytoplasm of proliferated mononuclear cells.

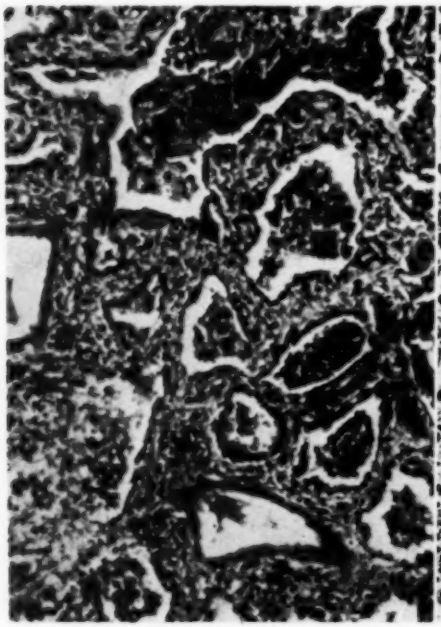

FIGURE 1

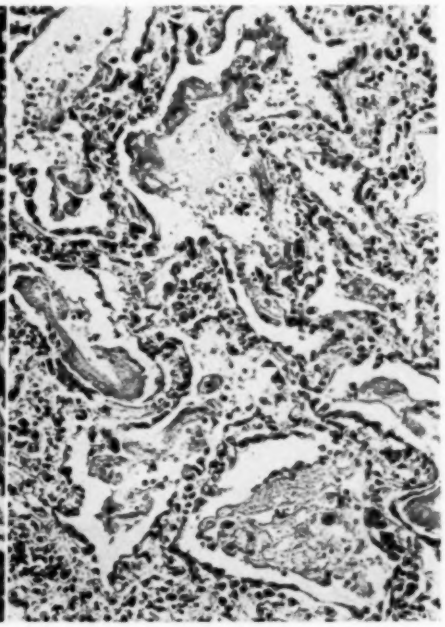

FIGURE 2

Figure 1: Interstitial pneumonitis in scrub typhus. The alveolar walls are markedly thickened by edema and mononuclear exudate, and alveolar lining cells are prominent. (A. I. P. neg. No. 82723).—*Figure 2:* Toxoplasmic pneumonitis. Mononuclear exudate thickens alveolar walls. With higher magnification, toxoplasma may be identified in the prominent alveolar lining cells.

ated epithelium. The bronchiolar epithelium is frequently partially eroded. The bronchiolar walls and adjacent radiating interstitial tissues are thickened by edema and infiltration by lymphocytes, plasma cells and macrophages. Alveolar lining cells become conspicuous, and in experimental animals rickettsiae have been observed in such cells. Evidence of fibroblastic proliferation in alveolar walls is common.

Toxoplasmic Pneumonitis

Toxoplasma is a protozoan which recently has been recognized as the causative agent in certain types of meningo-encephalitis of newborn infants. The circumstances suggest prenatal infection, and hence imply latent infection in the mothers.

At least three cases of acute toxoplasmosis in adults have been recognized.[7] They were characterized by a clinical picture similar to that of typhus or spotted fever, and the pathologic picture of interstitial pneumonitis. Death appeared to be due primarily to interference with respiratory function. The morphologic changes in the lungs are basically similar to the interstitial pneumonitis of atypical pneumonias. Important features, however, are a prominence of alveolar lining cells and a tendency to interstitial fibrosis.

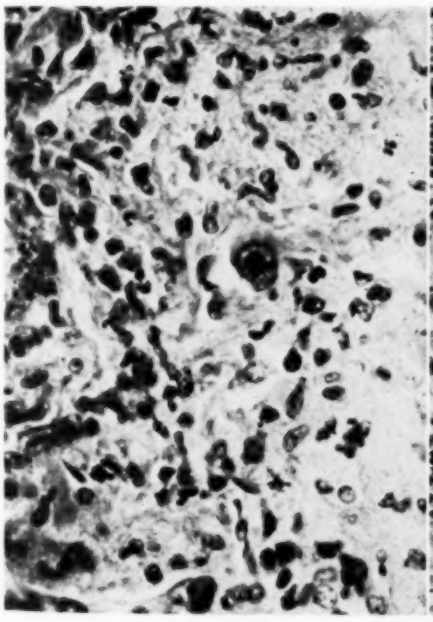

FIGURE 5

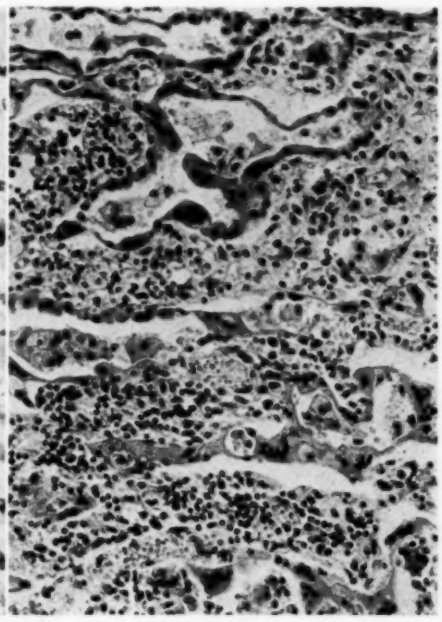

FIGURE 6

Figure 5: Pneumonitis in Inclusion Disease of Infancy. Note the large dark intranuclear inclusion, and the predominance of mononuclear cells in the exudate.—*Figure 6:* Giant cell pneumonia of infancy. In addition to the thickening of alveolar walls by mononuclear exudate, the hyperplastic alveolar lining cells have fused to form syncytial multinucleated giant cell forms.

Aveoli appear to be lined by cuboidal cells, in some of which the diagnostic toxoplasma may be found. The exudate of the alveolar septa tends to become organized, so that the thickened alveolar walls show early stages of fibrosis.

Histoplasmic Pneumonitis

Histoplasmosis is due to an encapsulated yeast-like fungus. While occurring predominantly in the phagocytic cells of the reticulo-endothelial system, it has manifested itself on occasion as a respiratory infection.

In one case observed by the author,[8] in an infant, the most prominent manifestation was a respiratory infection which persisted four months until the time of death, and which at times received the clinical and roentgenological interpretation of tuberculosis and of bronchitis and bronchopneumonia. The lungs showed a patchy chronic pneumonitis, the irregular thickening of alveolar walls being due to increase of monocytes and fibroblasts. The diagnostic encapsulated "histoplasma" were recognizable in many of the monocytic cells. Unlike other types of interstitial pneumonitis, however, involvement of blood vessel endothelium was a

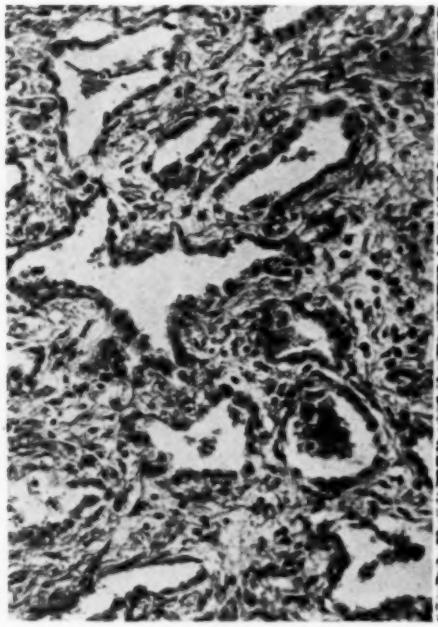

FIGURE 7

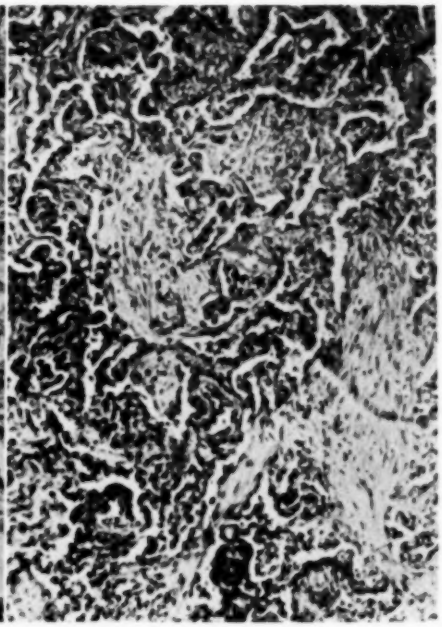

FIGURE 8

Figure 7: Acute diffuse interstitial pulmonary fibrosis. The thickening of alveolar walls is due mainly to overgrowth of fibroblastic tissue, and cellular exudate is relatively scanty. The alveolar lining cells are prominent.—*Figure 8:* Fibrosing or organizing pneumonia. In contrast to interstitial fibrosis, the fibroblastic overgrowth is the result of organization of exudate in alveolar spaces.

prominent and distinctive feature. In other cases of pulmonary histoplasmosis the histologic features have been more like those of tuberculosis or coccidiomycosis.

Viral Pneumonias of Infants and Children

In several types of pneumonia in infancy distinctive inclusion bodies characteristic of viral activity have been found. The so called "inclusion disease" described by Farber and Wolbach[9] and others is characterized by an interstitial pneumonitis with prominent alveolar lining cells. Some of the lining cells show large granular inclusions which distend the nuclei, and occasional smaller cytoplasmic inclusions. An epidemic variety with a mortality of about 20 per cent has been reported by Adams,[10] in which only cytoplasmic inclusions are seen.

Giant cell pneumonia, as described by Hecht[11] in 1910, is a rare but distinctive interstitial pneumonitis. It is characterized by large multinucleated giant cells formed by proliferation and fusion of cells lining alveoli, alveolar ducts, and bronchioles. Cytoplasmic inclusions, pleomorphic and often very large, are found in these cases, and also less numerous small nuclear inclusions.[12] The morphologic changes in the lungs, including the characteristic inclusions, are identical with those found in canine distemper in animals, and quite unlike that of any other known viral infection except early and uncomplicated measles pneumonia. This suggests a possible biological relationship of the viral etiology of giant cell pneumonia in man and canine distemper in animals. Also of particular interest is the fact that giant cell pneumonia is an interstitial pneumonitis in which the most prominent feature is a proliferation and metaplasia of alveolar and bronchiolar lining cells. This has features suggestive of the metaplastic changes in the respiratory tract found in Vitamin A deficiency.[13].

Acute Diffuse Interstitial Fibrosis of the Lungs

In 1944, Hamman and Rich[14] described under the title "acute diffuse interstitial fibrosis of the lungs" a condition with unusual clinical and anatomical findings. It was characterized by a peculiar, diffuse, progressive fibrosis of pulmonary alveolar walls, leading to deficient aeration of blood with resulting dyspnoea and cyanosis, and to enlargement and eventual failure of the right side of the heart. The alveolar walls were tremendously thickened, but with little cellular exudate in comparison with the usual interstitial pneumonitis. The alveolar walls were edematous and crowded by fibroblasts, which in late stages matured to dense scar tissue. Other changes which were essentially similar

to those of the usual interstitial pneumonitis included enlargement of alveolar lining cells, necrosis of alveolar and bronchiolar epithelium, and formation of a hyaline membrane that lines alveoli. Kneeland and Smetana,[15] in one of the early published reports on atypical pneumonia, included a case which was similar clinically and anatomically.

SUMMARY

The interstitial pneumonitis due to a variety of etiologic agents and circumstances has been commented upon to emphasize certain aspects not commonly stressed, namely, the common hyperplasia and metaplasia of alveolar and bronchiolar lining cells, and the tendency in many cases to progress to interstitial fibrosis. The changes which often cause cyanosis to be a prominent clinical feature would merit a separate complete and full discussion. One may speculate as to whether the present prevalence of atypical pneumonia may lead in the future to an increased clinical incidence of (1) effects of interstitial pulmonary fibrosis, and (2) pulmonary tumors resulting from stimulation of bronchiolar and alveolar lining cells. Only time will give the answer.

RESUMEN

Se han discutido las neumonitis intersticiales debidas a una variedad de agentes y circunstancias etiológicas a fin de hacer énfasis sobre ciertos aspectos que comúnmente no se recalcan, a saber, la hiperplasia y metaplasia comunes de las células alveolares y bronquiolares, y la tendencia de muchos casos de progresar a una fibrosis intersticial. Las alteraciones que frecuentemente causan que la cianosis sea un rasgo clínico prominente merecen una discusión completa y separada. Se puede meditar sobre la posibilidad de que la frecuencia actual de la neumonía atípica pueda conducir en el futuro a una creciente frecuencia clínica de (1) los efectos de la fibrosis pulmonar intersticial, y (2) tumores pulmonares debidos a la estimulación de células bronquiolares y alveolares. Sólo el tiempo lo podrá decir.

REFERENCES

1 MacCallum, W. G.: "The Pathology of Pneumonia in the United States Army Camps During the Winter of 1917-18," *Monograph 10,* Rockefeller Institute for Medical Research, 1919.
2 McCordock, H. A. and Muckenfuss, R. S.: "The Similarity of Virus Pneumonia in Animals to Epidemic Influenza and Interstitial Bronchopneumonia in Man," *Am. J. Path.*, 9:221, 1933.
3 Golden, A.: "Pathologic Anatomy of 'Atypical Pneumonia, Etiology Undetermined,'" *Arch. Path.*, 38:187, 1944.
4 Saphir, O.: "Pathological Changes in So-Called Atypical Pneumonia," *Radiology,* 40:339, 1943.
5 Reimann, H. A.: "The Viral Pneumonias and Pneumonias of Probable Viral Origin," *Medicine,* 26:167, 1947.

6 Allen, A. C. and Spitz, S.: "A Comparative Study of the Pathology of Scrub Typhus (Tsutsugamushi Disease) and Other Rickettsial Diseases," *Am. J. Path.*, 21:603, 1945.
7 Pinkerton, H. and Henderson, R. G.: "Adult Toxoplasmosis," *J.A.M.A.*, 116:807, 1941.
8 Anderson, W. A. D., Mickelson, I. G. and Dunn, T. M.: "Histoplasmosis in Infancy," *Am. J. Clin. Path.*, 11:344, 1941.
9 Farber, S and Wolbach, S. B.: "Intranuclear and Cytoplasmic Inclusions ('Protozoan-like Bodies') in Salivary Glands and Other Organs of Infants," *Am. J. Path.*, 8:123, 1932.
10 Adams, J. M.: "Primary Virus Pneumonitis with Cytoplasmic Inclusion Bodies," *J.A.M.A.*, 116:925, 1941.
11 Hecht, V.: "Die Riesenzellenpneumonie im Kindesalter," *Beitr. z. path. Anat. u. z. allg. Path.*, 48:263, 1910.
12 Pinkerton, H., Smiley, W. L. and Anderson, W. A. D.: "Giant Cell Pneumonia with Inclusions: A Lesion Common to Hecht's Disease, Distemper and Measles," *Am. J. Path.*, 21:1, 1945.
13 Chown, B.: "Giant Cell Pneumonia of Infancy as a Manifestation of Vitamin A Deficiency," *Am. J. Dis. Child.*, 57:489, 1939.
14 Hammon, L. and Rich, A. R.: "Acute Diffuse Interstitial Fibrosis of the Lungs," *Bull. Johns Hopkins Hosp.*, 74:177, 1944.
15 Kneeland, Y. and Smetana, H. F.: "Current Bronchopneumonia of Unusual Character and Undetermined Etiology," *Bull. Johns Hopkins Hosp.*, 67:229, 1940.
16 Parker, Frederic Jr., Jolliffe, L. S. and Finland, M.: "Primary Atypical Pneumonia: Report of Eight Cases with Autopsies," *Arch. Path.*, 44: 581, 1947.

Routine Fluororoentgen Chest Examinations of Hospital Admissions

From the Viewpoint of the Radiologist*

ABRAHAM MELAMED, M.D. and ALAN FIDLER, M.D.
Milwaukee, Wisconsin

The merits of chest surveys or screening by roentgen means cannot be disputed, provided adequate facilities and qualified professional personnel are available. The general principles governing such routine chest examinations, i.e., hospital admission screening, mass surveys, pre-employment and pre-induction examinations, are not dissimilar. While it is not the primary intent nor within the province of the authors to discuss the latter three categories, consideration of a few of the general principles governing such extensive routine chest examinations is timely. Physicians, particularly roentgenologists, and laymen are vitally concerned with and interested in this great problem.

There can be little doubt that most general hospitals of fair size will eventually institute a program of routine admission examination of the chests of all hospital and clinic patients. There has been considerable hesitancy on the part of hospital administrators and roentgenologists as a whole to adopt such measures. The latter group can exert inestimable influence in the advocacy of such programs. It is of prime importance that hospital administrators coordinate their efforts in sponsoring such programs. The principles so comprehensively analyzed by Garland[1] are worthy of consideration by all parties concerned. Hospital chest screening assumes even greater importance as an instrument in the development of facilities and supervision which can eventually be utilized and enlisted in mass surveys of the population.

Chest screening of all hospital admissions does not pose many of the difficulties inherent in a general mass survey. There is little to add to Hodges'[2] comprehensive analysis of the problems and results of routine fluororoentgen chest examinations of all hospital admissions. Our findings coincide with his statistics gathered in a general hospital. We concur with his expression that chest examinations in general hospitals can be made workable and effective without overloading or hampering the department of roentgenology. To say the least, chest diagnosis becomes more

*From the Department of Radiology, Evangelical Deaconess Hospital, Milwaukee, Wisconsin.

fascinating and valuable, especially as a part of a teaching program of a general hospital. It is interesting to find, as Hodges[2] observes in his paper, that the detection of tuberculosis does not comprise the main purpose of hospital surveys. The discovery of other unsuspected lesions assumes at least equal importance. Pulmonary tuberculosis in Hodges' and our series of hospital admission examinations constitutes approximately 10 per cent of all the abnormal and pathologic findings of clinical importance.

While a survey project can become incorporated in the general routine of hospital procedures without serious obstacles there are many problems which are worthy of consideration and must be solved before the program can be expected to function properly and efficiently. The main prerequisite is a certified roentgenologist in attendance who can provide proper supervision and interpretation of the films. Twenty-four hour service sooner or later is essential if any reasonable degree of success is to be attained so far as the percentage of admissions examined is concerned. To further implement the successful operation of the project the x-ray equipment is preferably housed adjacent to the admitting room.

At the Evangelical Deaconess Hospital, Milwaukee, Wisconsin, a plan to examine the chest of all hospital admissions was devised and approved in 1945 but the equipment did not arrive until 1947. At the inception of the program active and passive resistance was displayed by some of the members of the attending staff but this antagonism was soon abolished when the results of chest screening were divulged. All of the physicians now exhibit a lively interest in the program and the lesions uncovered. The chest films are interpreted the morning after admittance. The findings are always reported prior to scheduled surgery. In such manner a surgeon is often enabled to choose an optimum anesthetic agent under the prevailing cardiopulmonary conditions, thereby probably reducing morbidity and perhaps mortality to a minimum. In some instances operations are cancelled when the chest findings are disclosed. Many so-called early malignant lesions of the bowel, urinary tract, etc., when least suspected are not infrequently the cause of demonstrable metastatic lesions to the chest, as has been our experience in this work. There can be little doubt that the routine chest screening of hospital admissions is destined to assume equal, if not greater, status and importance than other routine laboratory analyses. Hodges[2] contends, and rightly so, that routine chest examinations of hospital and clinic patients will reveal more positive findings than serologic testing for syphilis, similarly applied.

We shall not delve into a detailed discussion of the advantages

and disadvantages of the various methods of chest screening. The problems vary in different institutions and communities. We have found the 4 x 5 inch stereo fluororoentgen film most suitable for our purposes. De Lorimer[3] analyzes the various methods of examination of the chest according to terms of trust for single case study, trust for mass studies, coordination with other examinations, future reference, unit cost per examination, and initial cost of equipment. His analysis led to official adoption of the stereoscopic technic with the 4 x 5 inch film for the United States Army.

Birkelo and his colleagues[4] present the results of a detailed investigation of the various methods of chest screening so far as effectiveness in tuberculosis case finding is concerned. They find that purely from the standpoint of effectiveness of tuberculosis case finding none of the methods, not even the 14 x 17 inch celluloid, is superior to the others. We favor, therefore, for purposes of a more general appraisal of the thoracic structures, the largest of the miniature films, so to speak, the 4 x 5 inch stereo. This method seems capable also of providing a fairly accurate eveluation of cardiac size when correction for distortion is made. Levitin[5] in his report of 10,000 chest examinations with stereoscopic photoroentgen equipment finds the 4 x 5 inch stereo film most satisfactory for chest survey, more economical than the 14 x 17 inch film, and having the same, if not better, diagnostic accuracy.

The interpretation of survey films is wrought with some danger. Birkelo and his associates[4] show that there are many inter- and intra-individual variations. They justly conclude that in mass surveys films should be read by at least two interpreters. At the Deaconess Hospital at least two and sometimes three examiners interpret the films independently. Not infrequently one or the other is found guilty of over- and underreading—paralleling the findings of Birkelo and his colleagues. If such interpretative ser-

TABLE 1

Number of Admissions: July 1, 1947 to March 15, 1948	4655
Number of fluororoentgen examinations of chest	3626
Percentage of admissions examined	77.8
No fluororoentgen examinations:	
Large chest film requested on admission.	
Chest film within six months prior to admission.	
Readmission—less than six month interval.	
Physical condition not permitting: coronary thrombosis, fracture cases, head injuries, cerebral accidents, etc.	
Patients refusing examination.	
Patients entering or leaving hospital when x-ray department closed.	

vices are not available it seems desirable for the roentgenologist to review the films at least once.

From July 1, 1947 to March 15, 1948, 3,626 fluororoentgen chest examinations have been performed at the Evangelical Deaconess Hospital, Milwaukee, Wisconsin. This number represents 77.8 per cent (Table I) of all hospital admissions during the same period. During the past few months our efficiency in this respect is greater; 80-85 per cent of all admissions are examined but it seems unlikely that this figure can be improved without 24 hour technical services.

TABLE 2

Number of examinations: July 1, 1947 to March 15, 1948		3626
	Per cent	*Cases*
Essentially negative findings	71.4	2591
Abnormal findings of little or no clinical significance	18.4	667
Abnormal and pathologic findings warranting further study by 14 x 17 inch films, etc.	9.4	342
Pathologic findings: diagnosis certain and no further studies necessary	.8	26

TABLE 3

Abnormal and Pathologic Findings

	Cases	*Per cent*
Heart, abnormal contour and/or enlargement	171	4.7
Aortic abnormalities: dilatation, tortuosity, arteriosclerosis, apparent absence	124	3.4
Superior mediastinal widening: substernal thyroid dilatation innominate artery, enlarged thymus	55	1.5
Pleural thickening	119	3.3
Pleural effusion	8	.2
Diaphragm: elevation, wavy, flattened	110	3.0
Rib abnormalities; metastasis, cervical, ect.	82	2.0
Scoliosis	85	2.0
Probably tuberculosis Probably active — 3 Probably inactive — 43	46	1.25
Pulmonary pathology, undetermined origin (Bronchiectasis, chronic pneumonitis, etc.)	39	1.00
Increased markings	123	3.3
Pneumoconiosis	2	.05
Emphysema	176	4.8
Metastasis, suggestive and definite	18	.5
Atelectasis, plate-like (Fleischner lines)	4	.1
Hilar enlargement	27	.75

Approximately 71.4 per cent of the total number examined were interpreted as essentially negative (Table 2). In 18.4 per cent abnormal findings were discovered but these findings were assumed to be of little or no clinical significance. Over 10 per cent of the patients examined showed abnormalities obviously of pathologic significance and clinical interest.

Almost 5 per cent of all patients examined showed abnormal cardiac contours and/or evidence of enlargement. Of these a good number were cases of prominence of the pulmonary conus in pregnant women. We find that many of the pregnant women registering at the hospital 6-8 weeks before expected delivery exhibit such pulmonary conus enlargement. It is interesting to relate that in two such patients pulmonary changes were described on registration but the warnings were unheeded. A few to several weeks later these same patients were admitted to the hospital with toxemias of pregnancy—pre-eclamptic. In our series of 3,626 chest examinations 46 patients, representing an incidence of approximately 1.25 per cent, showed changes consistent with or due to tuberculosis, some "unstable," 3 probably active. Two cases of pneumoconiosis are also listed. Metastatic lesions in the chest constituted an important group, most of which were unsuspected. Eighteen such cases were discovered. The management of these cases was altered in most instances. To our surprise at least 27 patients (0.75 per cent) displayed suggestive and definite hilar node enlargement, bilateral in many instances. Follow-up studies of such patients is imperative.

Chest screening is valuable in still another respect. The fluororoentgen study of the chest on admission provides a "control" film. Should occasion arise for subsequent chest studies, postoperatively or otherwise, comparison of the films provides an excellent basis for interpretation. Whereas previously equivocal findings or slight apparent deviations from the "normal" were discounted or at best considered indication for later studies, now any slight change or new development in the chest receives its due consideration, often permitting of more precise diagnostic statements and earlier diagnosis. Suitable treatment can thus be instituted at an earlier stage of the complication, thereby reducing morbidity.

Landau and Schorsch[6] state that from 8 to 22 per cent of all general hospital and clinic patients show disease in routine chest films. This percentage of positive findings is indeed higher than with any of the other accepted routine laboratory procedures.

In 1934 Hodges[7] made a test of the utility of routine x-ray surveying of all patients' chests during 14 consecutive working days. They developed the films, put them away for three months, and

at the end of this period interpreted the films. They delved into the hospital records of the patients to see whether or not the examination might have been helpful in the diagnosis. They found that as a group they had made a gross error of omission once every day during that 14 day period. They felt that the medical profession could not afford an error of that extent, if it could be avoided. Thus, admission chest films in many instances obviate unnecessary floundering with diagnostic methods. In this period of hospital bed shortages any acceleration of our diagnostic services in effect provides more available hospital days.

SUMMARY AND CONCLUSIONS

The routine chest screening of hospital admissions by the fluororoentgen method is practicable in most general hospitals where the x-ray department is directed by a certified roentgenologist. Such procedures yield results of at least equal, if not greater, magnitude than other routine hospital laboratory procedures.

Abnormal and pathologic conditions of the chest of clinical importance are discovered in approximately 10 per cent of chests examined in hospital screening programs. About 10 per cent of these pathologic findings are probably due to pulmonary tuberculosis. Although pulmonary tuberculosis represents a relatively small percentage of the clinically important findings such case detection in hospitals is extremely important for several reasons: (1) It minimizes exposure of other hospital patients to tuberculosis by providing reason for segregation or transfer. (2) It permits of early diagnosis and institution of proper therapy. (3) It minimizes exposure of hospital personnel to tuberculosis. (4) It provides valuable data in compensation matters and disputes.

Nontuberculous diseases of the chest in hospital surveys are of much greater frequency and probably of equal importance. Cardiac abnormalities, mediastinal tumors or widening, enlarged hilar nodes, metastatic lesions, etc., account for approximately 90 per cent of the pathologic conditions uncovered by this method.

Admission chest fluororoentgenograms provide at least one more advantage. The availability of so-called "control" films of the chest is of great value in those instances where chest complications develop during the hospital stay or even at a later date after discharge from the hospital. Comparison of the "control" films with subsequent roentgen studies affords criteria which often permit of unequivocal diagnostic statements. With such comparative roentgen studies of the chest diagnostic uncertainty is often reduced to a minimum.

The viewpoint of the roentgenologists as regards chest surveys or screening is no different from the viewpoint of the medical

profession in general; that is, to provide feasible, well planned and supervised programs. Such planning is mandatory if the procedure is not to be discredited and the reputation of the medical profession is to be sustained. It is imperative that the medical profession undertake and supervise such programs if leadership in public health matters is to be regained and retained.

RESUMEN Y CONCLUSIONES

El examen sistemático del pecho de las admisiones a los hospitales mediante el método fotoroentgenográfico es aplicable a la mayoría de los hospitales generales donde el departamento radiológico está dirigido por un roentgenólogo certificado. Tales procedimientos dan resultados por lo menos iguales, si no de mayor magnitud que cualquier otro procedimiento sistemático de laboratorio del hospital.

Se descubren estados anormales y patológicos del tórax de importancia clínica en aproximadamente el 10 por ciento de los pechos examinados en esos programas de exámenes en los hospitales. Un 10 por ciento de esos hallazgos patológicos se deben probablemente a la tuberculosis pulmonar. Aunque la tuberculosis pulmonar representa un porcentaje relativamente pequeño de los hallazgos de importancia clínica, el descubrimiento de esos casos en los hospitales es extremadamente importante por varias razones: (1) Reduce al mínimo la exposición de otros pacientes del hospital a la tuberculosis, pues suministra una razón para el aislamiento o la transferencia. (2) Permite el diagnóstico temprano y la aplicación de la terapia apropiada. (3) Reduce al mínimo la exposición del personal del hospital a la tuberculosis. (4) Suministra datos valiosos en cuestiones y disputas de indemnización.

En los censos de hospital las enfermedades torácicas no tuberculosas son de mucha mayor frecuencia y probablemente de igual importancia. Las anomalías cardíacas, los tumores o el ensanchamiento del mediastino, los ganglios hiliares hipertrofiados, las lesiones metastásicas, etc., representan aproximadamente el 90 por ciento de los estados patológicos que se descubren por este medio.

Los fotoroentgenogramas torácicos tomados durante la admisión tienen por lo menos una ventaja adicional. La disponibilidad de las llamadas películas torácicas "de control" es de gran valor en esos casos en los que ocurren complicaciones torácicas durante la estadía en el hospital o aún después de haber sido dados de alta del hospital. La comparación de las películas "de control" con estudios roentgenológicos subsiguientes suministra criterios que a menudo permiten declaraciones diagnósticas inequívocas.

Con tales estudios roentgenológicos torácicos comparativos, frecuentemente se puede reducir al mínimo la incertidumbre del diagnóstico.

El punto de vista de los roentgenólogos acerca de los censos radiográficos torácicos no difiere del punto de vista de la profesión médica en general, es decir, de proveer programas factibles, bien ideados y supervigilados. Es obligatorio hacer esos planes si se desea evitar que se desacredite el procedimiento y se quiere sustentar la reputación de la profesión médica. Es imperativo que la profesión médica lleve a cabo y supervigile tales programas para que pueda recobrar y retener la dirección de las cuestiones de sanidad pública.

REFERENCES

1 Editorial: "A Total Population Chest Survey," *Radiology*, 49:629, 1947.
2 Hodges, F. J.: "Fluorographic Examination of the Chest, A Routine Hospital Procedure," *Radiology*, 38:453, 1942.
3 De Lorimier, Alfred A.: "Mass Roentgenography of the Chest for the United States Army," *Radiology*, 38:462, 1942.
4 Birkelo, C. C., Chamberlain, W. E., Phelps, P. S., Schools, P. E., Zacks, D. and Yerushalmy, J.: "Tuberculosis Case Finding. A Comparison of the Effectiveness of Various Roentgenographic and Photofluorographic Methods," *J.A.M.A.*, 133:359, 1947.
5 Levitin, J.: "Ten Thousand Chest Examinations with the Stereoscopic Photoroentgen Unit," *Am. J. Roentgenol.*, 49:469, 1943.
6 Landau, G. M. and Schorsch, H. A.: "The Adult Silent Chest," *Radiology*, 50:37, 1948.
7 Hodges, F. J.: "The Adult Silent Chest," Discussion, *Radiology*, 50:42, 1948.

UNIVERSITY OF MICHIGAN LIBRARIES

The Combined Use of Streptomycin and Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis*

STANLEY H. HOFFMAN, CAPT., M.C., A.U.S.
GEORGE A. HYMAN, CAPT., M.C., A.U.S.
Denver, Colorado

Introduction

In this paper the authors are attempting to evaluate a combined mode of therapy for the treatment of pulmonary tuberculosis consisting of pneumoperitoneum and streptomycin. No attempt is being made to compare these two methods of treatment, but to see if a combination of the two is not the best means of therapy in certain types of cases. It has been our experience at Fitzsimons General Hospital that a number of cases of pulmonary tuberculosis with cavitation treated with streptomycin have shown good results during the course of treatment but a reappearance of cavitation upon the discontinuation of streptomycin. This has also been the experience of Hinshaw, Feldman and Pfuetze,[2] the cooperative study of Army, Navy, Veterans Administration,[5] and Canada.[6] D'Esopo and Steinhaus[12] also emphasize that relapses occur in a significant number of cases toward the end of treatment as well as shortly afterwards and felt "that there might be an optimum time during the course of therapy when the institution of collapse procedures might have preserved what improvement had occurred."

It has been our experience at Fitzsimons General Hospital that usually these cases with reopened cavities become positive for tubercle bacilli again and that in 70-80 per cent the organism is resistant to streptomycin in 100 micrograms per cubic centimeter. As shown by Fisher and his associates[7] this has occurred whether the dosage is 1.8 or 1.0 grams (Fisher[14]). Consequently we have been attempting to follow the successful or incomplete closure of cavities during streptomycin therapy with some type of temporary collapse measure. In this paper we are discussing the cases treated only with one type of collapse measure, namely pneumoperitoneum, and we hope to present pneumothorax used in conjunction with streptomycin in a later paper.

The indications for the type of temporary collapse measure selected are the same as cases untreated by streptomycin. In this

*From the Medical Service, Fitzsimons General Hospital.

series of cases pneumoperitoneum was used especially in cases with cavities notoriously difficult to close with other collapse measures, such as basilar and hilar cavities (Rafferty[17]). In addition the usual indications for pneumoperitoneum were used (Banyai[15]). Our primary criteria for the use of pneumoperitoneum were:

A) Pneumothorax unsuccessful or contraindicated.
B) Bilateral cavitary disease.
C) Diseases unsuitable for thoracoplasty.
D) Preparative for surgical procedures.

The authors are of the opinion that pneumoperitoneum should not be considered as a last ditch measure, or following the exclusion of all other collapse measures, but rather as a definitive measure in itself (Editorial,[18] "Diseases of Chest").

Crow and Whelchel[16] reported a series of 546 cases of pneumoperitoneum with diaphragmatic paralysis in which 63 per cent showed apparent closure of all cavities. Sixty-four per cent of these cases had far advanced disease. We will attempt to show in this paper that good results can be obtained by the use of adequate pneumoperitoneum in conjunction with streptomycin therapy.

Criteria for the Selection of Cases

This series is composed mainly of young white males on active duty in the armed forces or recently discharged. In addition it includes 2 females and several older males. In all cases sputum cultures were positive for Mycobacterium tuberculosis, and all cases were being actively treated with pneumoperitoneum at Fitzsimons General Hospital at the time of this study. Cases are usually kept at Fitzsimons General Hospital for only a relatively short period of time before being sent to a Veterans Hospital so that the length of time these cases were observed was by necessity limited. It was found that the average was approximately six months time and it should be emphasized that this is a short term study of the benefits of this combination of treatment. All of these patients were maintained on absolute bed rest or bed rest with lavatory privileges.

Technique

Streptomycin was administered in the following schedule of doses:

14 received 1 Gm/day divided into 2 daily doses for 45-60 days
6 received 1 Gm/day divided into 2 daily doses for 90-120 days
2 received 2 Gm/day divided into 5 daily doses for 60 days
7 received 2 Gm/day divided into 5 daily doses for 120 days
1 received 2 Gm/day every third day for 120 days

UNIVERSITY OF MICHIGAN LIBRARIES

7 received 2 Gm/day for 60 days decreased to 1 Gm/day another 60 days
4 received additional treatment with aerosol for 6-16 weeks

The cooperative study by Army, Navy, Veterans Administration[5] has shown that 1 gm. of streptomycin daily appeared to be quite as effective in pulmonary tuberculosis as the regimen of larger doses. In 1 case streptomycin was discontinued because of severe vertigo. Aerosol administration of streptomycin is not being used at this hospital any longer because of frequent sensitization of patients as well as nursing personnel that occurs during nebulization. Similar if not superior results to nebulization can be obtained by injection.[5]

Adequate pneumoperitoneum of the type recommended by Brock[19] consisting of refills of at least 1000 cc. of air weekly, and frequently semi-weekly, was used. In 18 cases this was aided by a phrenemphraxis of the more involved side in bilateral disease and the affected side in unilateral disease. In 1 case pneumothorax was an additional concurrent procedure. No abdominal supports were used. In a few cases insulin was given to promote appetite.

Monthly x-ray films, weight, sputum cultures and smears, and sedimentation rates were taken. Gastric washing cultures were obtained in those patients who did not have sputum or whose sputum was negative on smear or culture. Streptomycin sensitivity tests were performed on all cultures positive for tubercle bacilli after treatment with streptomycin. Apical, Bucky and laminogram x-ray films were taken as circumstances required.

Results

Fifty seven patients who have received treatment with pneumoperitoneum for pulmonary tuberculosis at Fitzsimons General Hospital during the year 1947-48 constitute this series. Of this group 37 cases received, in addition to pneumoperitoneum, a course of streptomycin therapy. The majority of these cases were observed for an average of six months time, the longest being 1½ years, the shortest being 2 months. Most of the cases were under treatment for far advanced pulmonary tuberculosis.

In the cases treated by pneumoperitoneum alone either there was no streptomycin available or the protocol for treatment did not include these cases at that time. As streptomycin became more available the frequency of its use as an adjunct to pneumoperitoneum in the treatment of far advanced pulmonary tuberculosis increased considerably. Consequently, only a few cases have been treated by pneumoperitoneum alone during the past 6 months.

Streptomycin in the treatment of far advanced tuberculosis was shown to be definitely beneficial by Hinshaw, Feldman and Pfuetze.[2]

Streptomycin in Conjunction with Pneumoperitoneum

Thirty-seven cases of pulmonary tuberculosis were treated with a combination of streptomycin and pneumoperitoneum. Of these 27 (73 per cent) were far advanced cases and 10 (27 per cent) were moderately advanced. There were no minimal cases in this series. Rapid spontaneous regression was not likely to occur in that most of the patients had been on routine bed rest for several months and had not improved. All patients had moderate to severe constitutional symptoms (Table I).

Of the 37 cases 20 were cases in which streptomycin was started at least 1 month prior to pneumoperitoneum; 8 in which pneumoperitoneum preceded streptomycin by at least 1 month; and 9 where both were instituted at approximately the same time.

In this group of cases, evidence that pulmonary cavities had closed was observed in 21 patients; cavitation persisted in 16 cases. Definite roentgenologic improvement was considered from very good to excellent in 21. Little or no roentgenologically demonstrable improvement was seen in 5 cases. Tubercle bacilli disappeared from the sputum in 24 cases. This was substantiated by sputum smears and cultures and gastric washing cultures. Sputum was not converted in 7 patients in spite of at least 6 months treatment (See Table II). An additional 6 under observation for less than 6 months remained positive. In no cases under treatment was progression of the disease observed. In 1 case the patient continued to show roentgenologic improvement although the Mycobacterium tuberculosis was found to be resistant to streptomycin. None of the patients in this series died.

Clinical improvement as evidenced by significant improvements in sedimentation rate, weight, sputum production, cough, increased appetite, and generalized well being was excellent in 20 cases or

TABLE I

Pneumoperitoneum in Conjunction with Streptomycin

	— SEX —		— COLOR —		
	M	F	White	Negro	Others
Number	34	3	29	5	3
Per cent	92	8	79	13	8

	— AGE —				CLASSIFICATION			SPUTUM BEFORE TREATMENT	
	Teen	20-29	30-39	40-50	Min.	Mod. Adv.	Far Adv.	Pos.	Neg.
Number	6	17	10	4	0	10	27	37	0
Per cent	16	46	27	11	0	27	73	100	0

UNIVERSITY OF MICHIGAN LIBRARIES

54 per cent and good in 12 cases or 33 per cent. This was one of the most striking features of this study.

Of the 20 cases in which streptomycin was followed by pneumoperitoneum, it was found that 15 obtained no cavity closure on streptomycin alone but that in those cases in which pneumoperitoneum was induced within 2 months following the course of streptomycin, the following results were obtained:

1 closed cavity 0-1 month after pneumoperitoneum induced
7 closed cavity 1-2 months after pneumoperitoneum induced
1 closed cavity 2-3 months after pneumoperitoneum induced

TABLE II

Clinical Summary of 37 Cases Treated with Streptomycin and Pneumoperitoneum

	Streptomycin followed by Pneumoperitoneum	Pneumoperitoneum followed by Streptomycin	Started Together	Total	Per cent
Number of cases	20	8	9	37	100
Sputum converted	13	3	8	24	65
Sputum not converted	7	5	1	13	35
Cavities:					
Closed	13	2	5	20	56
Smaller	5	2	2	9	24
Unchanged or Worse	2	4	1	7	19
Roentgenologic Improvement:					
Excellent	12	3	6	21	57
Good	7	1	3	11	30
Slight	1	1	0	2	5
None or worse	0	3	0	3	8
Clinical Improvement:*					
Excellent	12	2	6	20	54
Good	7	2	3	12	33
Moderate	1	2	0	3	7
Slight	0	1	0	1	3
Unchanged or worse	0	1	0	1	3

*Sedimentation rate, weight, sputum production, fever, increased appetite, and cough.

1 closed cavity 4-5 months after pneumoperitoneum induced
1 closed cavity over 6 months after pneumoperitoneum induced
4 obtained no cavity closure

In this group of 15 cases with no cavity closure, 10 showed complete cavity closure within 6 months of pneumoperitoneum treatment. Of the 4 cases that failed to close cavities, 2 had been on pneumoperitoneum for only one month at the time this paper was written.

In another group consisting of 4 patients with pneumoperitoneum from 2-6 months following streptomycin, 2 closed their cavities within 3 months of pneumoperitoneum treatment and 2 have failed to do so.

The last of these 20 cases closed his cavity on streptomycin alone after 3-4 months treatment. The pneumoperitoneum was induced in this patient before the streptomycin was discontinued to maintain cavity closure. It is felt that this has been accomplished.

Nine patients were treated with streptomycin and pneumoperitoneum started simultaneously. This group showed the most favorable results. Five cases showed cavity closure on x-ray examination. One case had no cavities but had extensive disease. Three cases showed no definite cavity closure on the x-ray film. In two of these cases the presence of cavitation was equivocal, but since there has been some doubt, they were included as incomplete

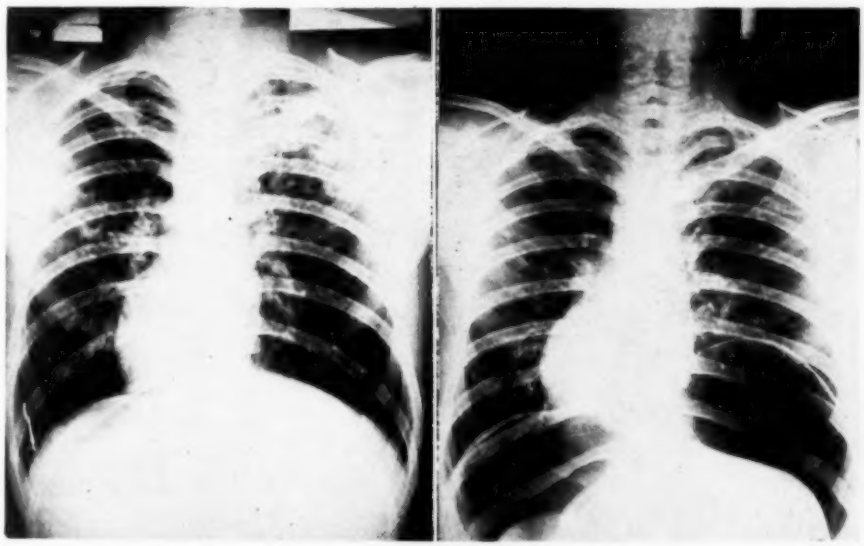

FIGURE 1 FIGURE 2

Figure 1, Case I: X-ray film No. 1, taken March 18, 1947, before pneumoperitoneum or streptomycin started.—*Figure 2, Case I:* X-ray film No. 2, taken July 29, 1947, showing marked clearing bilaterally. No evidence of cavitation. Patient had been on combined treatment of pneumoperitoneum and streptomycin for approximately two months.

UNIVERSITY OF MICHIGAN LIBRARIES

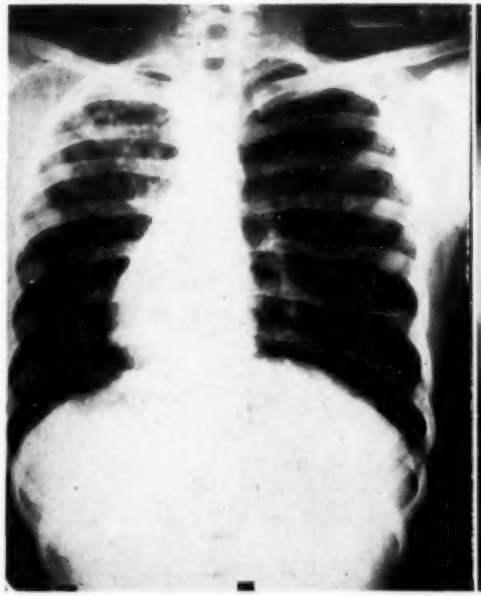

FIGURE 1

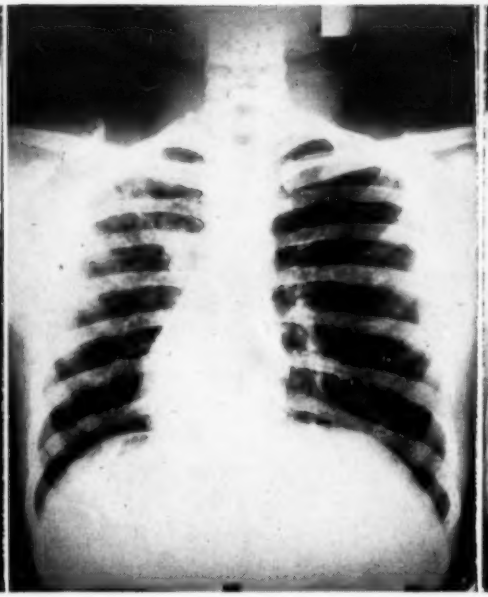

FIGURE 2

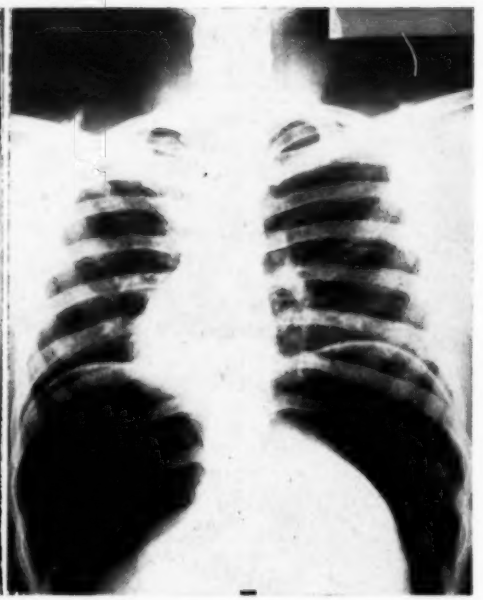

FIGURE 3

Figure 1, Case II: X-ray film No. 1, taken November 7, 1947, before pneumoperitoneum or streptomycin started.—*Figure 2, Case II:* X-ray film No. 2, taken January 27, 1948, after six weeks of treatment with streptomycin. Residual cavitation remaining in left upper lobe. Streptomycin was discontinued at the time this film was taken.—*Figure 3, Case II:* X-ray film No. 3, taken February 24, 1948, after one month of pneumoperitoneum, showing further regression of infiltration in left upper lobe. No evidence of cavitation.

cavity closure. However, both of these cases have been negative in sputum examinations for several months.

The third group of 8 patients under observation was treated by pneumoperitoneum and was followed in 1-12 months by streptomycin therapy. This group showed the poorest results. Four patients showed no cavity closure on streptomycin, but 1 patient closed his cavity 2-3 months following a course of streptomycin while on pneumoperitoneum. Of the remaining 4 patients, 2 showed cavity closure within 4-5 months following streptomycin while on pneumoperitoneum. The poor results of this group may be explained on the basis of the long duration of far advanced disease from which all of these patients suffered. This group demonstrates the advisability of using streptomycin early in the course of the disease, if good results are to be expected.

It is felt that the following case is a rather typical one and shows the excellent results that can be expected by this combined treatment. Another x-ray illustration is shown, but the case is not being presented for the sake of brevity.

Case 1: This 21 year old white male was admitted to Fitzsimons General Hospital on April 2, 1947 with a history of the onset of his disease in February 1947, with severe constitutional symptoms. He had a cough productive of ¾ cup of sputum, positive on smear and culture for tubercle bacilli. Temperature was 100 degrees F. Sedimentation rate was 29 mm./hr. (Wintrobe). X-ray film on admission revealed an exudative area of infiltration in the right upper lobe with two cavities measuring 2 x 2.5 cm., one in the 1st interspace and the other under the 2nd anterior rib. Exudative-caseous disease involved all lobes of the left lung, but was most extensive in the 2nd, 3rd, and 4th interspaces. A cavity 2.5 x 3 cm. was present in the 2nd interspace on the left (See Fig. 1). A right pneumothorax was attempted on April 9, 1947 but was unsuccessful. On April 25, 1947 streptomycin (2 gm./day, divided into 5 doses) was started. On May 16 a pneumoperitoneum was induced and on May 31, 1947 a right phrenemphraxis was added. Streptomycin was discontinued on August 25, 1947.

Temperature became normal 3 weeks after streptomycin was started and in July 1947 sedimentation rate was normal. There was a marked improvement in the cough at this time and he produced only 4-15 cc. sputum in 24 hours. Sputum has been negative on smear and culture since July 1947.

X-ray film taken at the conclusion of streptomycin therapy showed remarkable clearing with no definite evidence of cavitation visible. A substantial pneumoperitoneum was present. He continued to show clearing on x-ray examinations even though the streptomycin was discontinued, and by January 1948 there were only a few fibrous strands visible.

Twenty cases were treated by pneumoperitoneum alone (See Tables III and IV). Fourteen cases were treated for less than 6 months. Five of these cases obtained cavity closure as seen on x-ray films and in 7 additional cases there was significant de-

UNIVERSITY OF MICHIGAN LIBRARIES

crease in cavity size. Thirteen of these cases had a positive sputum before treatment and 8 have obtained sputum conversion.

Six cases were treated for more than 6 months. Of these 2 obtained cavity closure and 2 had significant decrease in cavity size. Two cases had sputum conversion with all six being positive originally.

Discussion

It is important to realize that we are not attempting to compare pneumoperitoneum alone with a combined method of pneumoperitoneum and streptomycin. The only reason we included those cases treated by pneumoperitoneum alone was to demonstrate the type of results that are obtained at Fitzsimons Hospital when only

TABLE III

Pneumoperitoneum Alone

	TOTAL CASES	SEX		COLOR	
		Male	Female	White	Negro
Number	20	19	1	16	4
Per cent	100	95	5	80	20

	AGE				CLASSIFICATION		
	Teen	20-29	30-39	40-49	Min.	Mod. Adv.	Far Adv.
Number	0	12	7	1	0	8	12
Per cent	0	60	35	5	0	40	60

TABLE IV

Pneumoperitoneum Only Treatment

	Total No. of Cases	Cavity Closure	Cavities Significantly Decreased in Size	Unchanged	Sputum Conversion	Negative Before Treatment	Positive Before Treatment
Under 6 Mos.	14	5	7	2	8	1	13
Over 6 Mos.	6	2	2	2	2	0	6

	Improvement X-Ray	Improvement* Clinical
Excellent	7	5
Moderate	6	9
Slight	5	3
Unchanged or worse	2	3

*Sedimentation rate, weight, sputum production, fever, increased appetite, and cough.

pneumoperitoneum is used. Cavity closure was obtained by only one-third of the cases we presented where streptomycin was not used. We realize that this is only a short term observation and that some of these cases might later show cavity closure. When streptomycin was used, cavity closure rate was almost doubled, with 57 per cent obtaining closure and 65 per cent sputum conversion. In addition 87 per cent of our cases showed either good or excellent x-ray evidence of regression of lesions when treated with combined therapy. We feel that this is of significance.

In the group of cases treated by pneumoperitoneum unsuccessfully and followed by a course of treatment of streptomycin, less satisfactory results were obtained. This may be explained by the interval elapsing between the onset of disease and institution of therapy. The authors are of the opinion that this series indicates that better results can be obtained if early combined treatment is instituted, in view of the results presented in tables I and II.

We feel that this paper is a further tribute to the value of streptomycin in the treatment of pulmonary tuberculosis, but that the startling results in many of these cases were not due to streptomycin alone. This is best shown by the group of 15 cases that did not show cavity closure on streptomycin but in which 10 showed complete cavity closure within 6 months post-streptomycin while on pneumoperitoneum. In addition there was one case whose cavity closed during the 3rd month of streptomycin therapy and in which we believe that pneumoperitoneum was instrumental in maintaining cavity closure. These findings are in line with the data presented by D'Esopo and Steinhaus[12] in which they conclude that "The infrequency of cavity closure suggested the use of streptomycin as an adjunct to collapse procedures."

Good results were obtained in two of our methods of treatment, namely, (a) streptomycin followed by pneumoperitoneum, (b) streptomycin and pneumoperitoneum introduced simultaneously. Although pulmonary physiology studies reveal a decreased circulation to a partially relaxed lung which in turn might mean a lessened amount of streptomycin brought to the diseased tissue, this was not apparently significant in view of the good results that were obtained in our series. It remains for future observation to determine the optimal time for the introduction of pneumoperitoneum or other collapse measures in relation to streptomycin. We think that the trend of therapy in pulmonary tuberculosis will be toward early collapse of cavitary lesions accompanied by a course of streptomycin at approximately the time the collapse measure is instituted. This may save the patient months if not years of hospitalization.

Five cases with extensive bilateral cavitary disease were made

UNIVERSITY OF MICHIGAN LIBRARIES

ready for surgical procedures, such as thoracoplasty or extrapleural pneumonolysis with lucite balls. This surgery may eventually result in cure of their disease. The probable ultimate salvage of these cases is rather encouraging in view of the hopeless outlook for these patients when they were first hospitalized and started on the pneumoperitoneum-streptomycin treatment.

SUMMARY

1) This is a series of 57 cases of pulmonary tuberculosis in predominately young white males treated at Fitzsimons General Hospital during 1947-1948.

2) Thirty nine far advanced cases and 18 moderately advanced cases were observed. No minimal cases are included in this series.

3) Thirty seven cases were treated with a combined program of streptomycin plus pneumoperitoneum.

4) This group was subdivided into:

(a) Twenty cases treated with streptomycin followed by pneumoperitoneum.

(b) Eight cases treated with pneumoperitoneum followed by streptomycin.

(c) Nine cases treated with streptomycin plus pneumoperitoneum started simultaneously.

5) In group (a) 13 had sputum conversion and 13 had cavity closure. In group (b) 3 had sputum conversion and 2 had cavity closure. In group (c) 8 had sputum conversion and 6 had cavity closure.

6) Twenty cases were treated with pneumoperitoneum alone and are included to demonstrate the type of result to be expected by this treatment.

7) The results seem to indicate that the best treatment for far advanced and moderately advanced cases, not suited for major surgery and in whom pneumothorax is not indicated, is the combined use of streptomycin and pneumoperitoneum as early in the course of the disease as possible.

RESUMEN

1) Se presenta una serie de 57 casos de tuberculosis pulmonar en hombres predominantemente jóvenes y blancos, tratados en el Hospital General Fitzsimmons durante el período de 1947 a 1948.

2) Se observó a 39 casos muy avanzados y 18 moderadamente avanzados. No se incluyen casos mínimos en esta serie de casos.

3) Se trató a 37 casos con un programa combinado de estreptomicina y neumoperitoneo.

4) Se subdividió a este grupo en:

(a) Veinte casos tratados con estreptomicina seguida de neumoperitoneo.

(b) Ocho casos tratados con neumoperitoneo seguido de estreptomicina.

(c) Nueve casos tratados con estreptomicina y neumoperitoneo comenzados simultáneamente.

5) En el grupo (a) en 13 se convirtió el esputo y en 13 se cerraron cavernas. En el grupo (b) en 3 se convirtió el esputo y en 2 se cerraron cavernas. En el grupo (c) en 8 se convirtió el esputo y en 6 se cerraron cavernas.

6) Se trató a 20 casos con neumoperitoneo solo y se los incluye para demostrar la clase de resultado que se puede esperar con este tratamiento.

7) Los resultados parecen indicar que el mejor tratamiento para casos muy avanzados y moderadamente avanzados, no adaptables para la cirugía mayor y en los que no está indicado el neumotórax, es el uso combinado de la estreptomicina y el neumoperitoneo tan temprano en la evolución de la enfermedad como lo sea posible.

REFERENCES

1 Waring, J. J.: "Pulmonary Diseases," *J.A.M.A.*, 136:311, 1948.
2 Hinshaw, H. C., Feldman, W. H. and Pfuetze, K. H.: "Treatment of Tuberculosis with Streptomycin," *J.A.M.A.*, 132:778, 1946.
3 Sanford, H. N. and O'Brien, D. E.: "Treatment of Tuberculosis with Streptomycin," *J.A.M.A.*, 132:669, 1946.
4 Pfuetze, K. H.: "Treatment of Tuberculosis with Streptomycin," *J.A.M.A.*, 132:648, 1946.
5 Preliminary Report of a Cooperative Study of 223 Patients by the Army, Navy, and Veterans Administration: "Effect of Streptomycin Upon Pulmonary Tuberculosis," *Amer. Rev. Tuberc.*, 56:485, 1947.
6 Canada, R. O.: "Streptomycin Therapy in Progressive Pulmonary Tuberculosis, Preliminary Report of Clinical Investigation in 37 Patients," *Amer. Rev. Tuberc.*, 56:508, 1947.
7 Fisher, M. W., Fishburn, G. W. and Wallace, J. B.: "Streptomycin and Bed-Rest in the Treatment of Pulmonary Tuberculosis," *Amer. Rev. Tuberc.*, 56:534, 1947.
8 Shamaskin, A., Morris, L. C., Des Autels, E. J., Mindlin, J., Zvetina, J. R. and Sweany, H. C.: "Streptomycin in the Treatment of Pulmonary Tuberculosis, Report of 15 Patients," *Amer. Rev. Tuberc.*, 56:540, 1947.
9 Cassidy, W. A. and Dinner, E.: "Pulmonary Tuberculosis Treated with Streptomycin, A Report of 20 Patients," *Amer. Rev. Tuberc.*, 56:552, 1947.
10 Parnall, C. Jr., Brock, B. L. and Moyer, R. E.: "Streptomycin in the Treatment of Pulmonary Tuberculosis, A Therapeutic Review of 23 Patients," *Amer. Rev. Tuberc.*, 56:565, 1947.
11 Allison, S. T. and Nilsson, J. M. N.: "Treatment of Pulmonary Tuberculosis with Streptomycin," *Amer. Rev. Tuberc.*, 56:579, 1947.
12 D'Esopo, N. D. and Steinhaus, J. E.: "Streptomycin Therapy, with Special Reference to Pulmonary Tuberculosis," *Amer. Rev. Tuberc.*, 56:589, 1947.
13 Riggins, H. M. and Gearhart, R. P.: "Chemotherapy of Tuberculosis," *Amer. Rev. Tuberc.*, 57:35, 1948.
14 Fisher, M. W.: Personal Communication to the Authors.
15 Banyai, Andrew L.: "Pneumoperitoneum Treatment," *C. V. Mosby Co.*, p. 202, 1946.
16 Crow, H. E. and Whelchel, F. C.: "Diaphragmatic Paralysis and Pneumoperitoneum," *Amer. Rev. Tuberc.*, 52:367, 1945.
17 Rafferty, T. N.: "Artificial Pneumothorax in Pulmonary Tuberculosis," *Grune Co.*, 1944.
18 Editorial, *Dis. of Chest*, 13:387, 1947.
19 Brock, B. L.: Address at Annual Meeting of the American College of Chest Physicians," 1946.

Propagating Pulmonary Artery Thrombosis*
(A Specific Syndrome*)

WILLIAM J. BRYSON, M.D.
Baltimore, Maryland

In considering pulmonary vascular occlusion, one often neglects propagating thrombi of the main stem and right or left branches of the pulmonary artery. The attention is usually centered upon pulmonary embolism which results in infarction or sudden death. There is, however, a specific syndrome that is produced by thrombosis of the pulmonary trunk or it's right and left branches. The thrombus by propagation gradually reduces blood flow through the pulmonary arterial tree and concomitantly resists outflow from the right ventricle. For purposes of clarity, the pulmonary arterial tree is divided into (a) the pulmonary trunk and its two branches, (b) the lobar divisions, and (c) the lobular arteries. Thrombosis occurs most commonly at site (c) (lobular branches) as the result of vascular obliteration by pulmonary disease. Rarely thrombosis occurs in position (b) (lobar branches) and may cause infarction or death. This discussion is concerned with progressively propagating thrombi at site (a) (pulmonary trunk and its two main branches) and the resultant specific syndrome which develops secondary to the blockage of blood flow through the entire lung.

The condition was first reported by Heile in 1837[1] and as early as 1897 Dickinson[2] was aware that the condition occurs even in young children. However, by 1934, only 26 cases had been reported in the literature.[1] In recent years many additional cases have been recognized and reported. The standard medical texts merely imply that pulmonary artery thrombosis is rare, but Harvey and Hogg[3] stated that the incidence falls between 0.9 per cent and 0.7 per cent when computed on the basis of necropsy reports. It is well recognized that even though the condition has occurred in a two year old child it is much more common in individuals who have progressed beyond middle life. Middleton,[4] who bases his statements on 53 necropsy cases, feels that the situation develops more frequently in men than in women. He gives a ratio of 3.4 to 1.

Roughly one-half of the cases have an acute onset and the remaining one-half develop slowly. Actually the duration has

*From the Department of Pathology, School of Medicine, University of Maryland, Baltimore, Maryland. Aided by a grant from the Sydney M. Cone Research Fund.

ranged from a few minutes to that of one or more years. Of the cases that the author reviewed, the longest in duration was one and one-half years[5] but it was not uncommon for the patient to remain alive for a four week period. About 10 per cent of the cases die in the first 12 hours and the remainder may live 10 days or more.[4]

The clinical symptoms show variation but nearly all of the cases, regardless of etiology, will show dyspnea. In the cases reported by Middleton, 90 per cent had dyspnea, 50 per cent had hemoptysis, 50 per cent had cyanosis, 25 per cent had cough, 25 per cent had pain in the chest or in the epigastrium, 25 per cent were apprehensive, and 20 per cent developed shock. Pou and Charr[6] in arranging the symptoms in order of frequency composed the following: dyspnea, cyanosis, engorged cervical vessels, pain in the chest or in the epigastrium, restlessness and mental confusion, exophthalmos and blurred vision, right heart failure with terminal edema. It is apparent that there are discrepancies between the two lists and actually many of the other cases reported failed to have some of the symptoms or had additional ones.[7-16] Thus, while it is admitted that considerable variations exist, the constant finding is that of dyspnea and most of the cases have cyanosis and others may have any of the above listed symptoms. If the onset is acute the patient is more apt to have dyspnea, cyanosis, chest pain, vomiting and signs of acute collapse, but if the condition develops gradually he will complain of dyspnea, cyanosis, cough and hemoptysis.

The dyspnea is extremely severe, out of proportion to that seen in cardiac failure and the cyanosis is so intense that it has been related to the cyanosis seen in Ayerza's disease.[6] The cyanosis begins in the head, particularly in the lips, nose and ears, and then involves the upper extremities causing bluish discoloration of the nailbeds. These conditions result from the reduction in the amount of blood that reaches the lungs.

As stated before, the pain may or may not be present and when it does occur it will not necessarily herald the difficulty but usually follows the dyspnea and cyanosis. Variation in the location of pain exists in that it may be beneath the sternum or in the epigastrium but it does not radiate. Finally, it may be excruciating or it may be a dull ache. A theorectical explanation for the abdominal pain is that is occurs as a result of an abnormal vagus reflex.[4] Restlessness and mental confusion, the results of anoxemia, occur uncommonly.

Considerable confusion exists concerning the character of the pulse pressure. It is reported to range from normal to very low. It can be said that the pulse pressure and the systolic pressure

are not affected to any marked degree in most cases. Hemoptysis results from congestion of the pulmonary vascular bed as a result of anastamosis between the pulmonary vessels and the bronchial arteries in an attempt to circumvent the block.[17] When the patient expires quickly, the engorged cervical veins and terminal edema which are manifestations of right heart failure do not develop. However, eliminating accessory causes for death, the chronic cases will die with right heart failure.

The thrombus causing this syndrome begins at the distal end of the right and left branches of the pulmonary artery and propagates retrogradely to the main bifurcation of the vessel but it may begin at the same site and propagate in the direction of the lung. About four-fifths of the lumen may be obstructed. In one-half of the cases the thrombus will ultimately end in bilateral involvement. Savacool and Charr[18] feel that in the great majority of cases the thrombus begins in the right artery. They were able to find only six cases of left pulmonary thrombosis. However, other investigators feel that the site of origin is equally divided between the right and left branches of the pulmonary artery.[4] This discrepancy may exist because all of the opinions concerning the site of origin are based on an attempt to tell the age of a particular part of the thrombus by its microscopic appearance. In chronic cases the thrombus often shows organization but this does not necessarily indicate its oldest part.

Many associated pathologic conditions are found in addition to the thrombus. Fifty per cent of Savacool and Charr's cases were complicated by some type of pulmonary disease and in a great many of their cases pulmonary arteriosclerosis was found. Other investigators feel that the outstanding associated pathologic lesions could be grouped under cardio-vascular disease with arteriosclerosis being the most important member of the group.[4] If a list were to be prepared it would include mitral stenosis, tuberculosis, arteriosclerosis of the pulmonary artery, silicosis, bronchitis, lung abscess, myocardial degeneration, congenital heart disease, thrombophlebitis, coronary heart disease, and tumors of the mediastinum.

Nearly all the chronic cases show hypertrophy and dilatation of the right ventricle and perhaps hypertrophy of the left ventricle as well.

It is obvious from the above discussion that pulmonary artery thrombosis is a secondary complication of some pre-existing pathologic state and that the pathogenesis will vary depending upon the original disease. Basically, while secondary factors may determine the site of formation of any thrombus, the condition is produced by either alteration of the vessel wall or disturbance in blood coagulation. Consequently, chronic pulmonary disease will

predispose to the development of pulmonary artery thrombosis by two methods: First, the chronic disease by destroying the lung and capillary tissue ultimately increases the pulmonary arterial pressure and thus influences the development of arteriosclerosis[19] which in turn damages the vessel wall. Secondly, the chronic disease by causing obliterative endarteritis slows pulmonary circulation and thus influences the blood coagulation. Pou and Charr[6] feel that in their cases the thrombus always began in the vessel passing to the lung containing a lesion and in cases of bilateral pulmonary disease the thrombus began in the vessel passing to the more involved lung.

In cases associated with thrombophlebitis, it is thought that a pulmonary embolus develops and then a thrombus is superimposed upon the embolus. Over a period of time the thrombus builds up in a retrograde fashion and becomes organized.[15] Finally, the thrombus may develop secondarily to congenital heart disease, rheumatic fever, bacterial endocarditis, polycythemia, and tumor invasion of the pulmonary artery.

Experimentally in dogs the systemic pressure will not fall until 60 per cent occlusion occurs to the pulmonary artery and death does not intervene until roughly 90 per cent of the lumen is blocked.[20] These experimental data may explain the progressive syndrome in chronic cases having a gradual onset. In addition, the collateral circulation which is said to develop between the bronchial arteries and the pulmonary vessels[17] may compensate for a time, but when near complete blockage of the pulmonary artery occurs, the patient dies because blood enters the right heart but cannot leave it. However, if a patent septum exists, blood may pass from the right ventricle to the left ventricle, allowing the patient to live longer but he will show deep cyanosis.[3] At the necropsy table it has been frequently noted that the thrombus almost completely blocks the vessel and yet microscopic organization can be seen indicating that the pathologic alterations have existed for a considerable length of time.

Electrocardiographic tracings are not diagnostic but are of negative value. McGinn and White[21] found prominent Q waves in lead one and late inversion of the T wave with a high takeoff in lead three. Wade[9] had a case that showed slight depression of the S-T segments, and in the case reported from the Massachusetts General Hospital, such changes as right axis deviation, flat S-T segments, right bundle branch block and low voltage of the QRS complex were noted.[13]

Fluoroscopy and chest roentgenograms are of more value, in that these patients show a prominence of the pulmonary conus and of the pulmonary artery.

Cardioangiography is in its infancy, and although the author knows of no reported cases of pulmonary artery thrombus in which the procedure was employed, in his opinion such a method should materially aid in the diagnosis, particularly in chronic cases. The pulmonary conus and the pulmonary artery with its branches have been completely and clearly demonstrated by several investigators working with cardioangiography and any block should be detected readily.

The differential diagnosis of congenital heart disease is of particular importance in children and young adults. Usually the patients with congenital heart disease have a history of a very prolonged illness, but in the opinion of Harvey and Hogg[3] if a sudden increase in the severity of the symptoms should occur, one must suspect superimposed thrombosis of the pulmonary artery.

In pulmonary embolism, the cyanosis and substernal or epigastric pain are not as severe as is seen in pulmonary artery thrombosis. Chest roentgenograms and a careful history are of great value.

Differentiation from coronary thrombosis is based on the history and the electrocardiographic, fluoroscopic and roentgenographic studies.

Case Report

The following case was seen at the University Hospital and represents a fairly typical example of the syndrome.

A white male, age 52 years, was admitted to the University Hospital September 14, 1947, and died September 16, 1947. He gave a history of periodic episodes of cyanosis and dyspnea since childhood and the patient had been told that he had congenital heart disease. Except for occasional attacks of dyspnea and cyanosis, he was not incapacitated and was employed as a barber. There was no history of exertional dyspnea, but the patient had mild anginal pain for a long time and evening swelling of his feet. However, when the edema disappeared by morning, he attributed the swelling to his occupation.

In July 1947, the patient had a severe bout of dyspnea, cyanosis, and edema of his ankles. He was placed at bed rest and remained there for one week. Subsequently the edema disappeared and the cyanosis lessened so the patient started back to work for short periods of time.

On September 12, 1947, he noticed severe fatigue and when the dyspnea and cyanosis progressed in degree, the patient retired to bed. By September 14, 1947, he appeared at the hospital complaining of cough, marked dyspnea, deep cyanosis, mild ankle edema and a temperature of 101 degrees F.

On examination it was noted that the patient was in marked respiratory distress with deep cyanosis of the skin and mucous membranes. The lips and nail beds were particularly blue. There was no distention of the cervical vessels. The percussion note was flat over the lower left chest and the heart was enlarged to the anterior axillary line. The cardiac rhythm was regular, the rate was 100 beats per minute and the

blood pressure was 130 mm. of mercury over 80 mm. of mercury. A palpable systolic thrill was present in the second and third interspaces about 6 cm. to the left of the mid-sternum and a very loud systolic murmur was heard in this area. The liver was palpable and there was mild pitting edema of the ankles.

On roentgenographic examination, the film showed diffuse infiltration of the entire left lung with some infiltration in the right mid-lung field and in the right lower lobe. The urine was negative, the serologic test for syphilis was negative and complete blood studies were negative except for a 10,850 white blood cell count and a differential count showing 95 per cent polymorphonuclear leucocytes. The sputum cultures were positive for streptococcus viridans, staphylococcus albus and diplococcus pneumoniae, but repeated sputum cultures were only positive for escherichia coli. The blood cultures were negative.

The electrocardiogram was not characteristic of any particular syndrome, but there were some aberrant T waves. The voltage was normal.

During the course of the disease, the patient was treated with sedatives, penicillin and oxygen; and although the temperature returned to 99 degrees F. in 24 hours and the chest signs cleared, the dyspnea increased so that the patient was breathing at a rate of 35 excursions per minute. The cyanosis remained and gradually increased until the patient expired on September 16, 1947, two days after admission.

At necropsy, the pathologist noted marked distention of the cervical vessels and deep cyanosis of the conjunctivae, nasal and oral mucosa and the skin of the upper and lower extremities. There was no pitting edema present, but the liver was enlarged to 8 cm. below the costal margin. The heart was enlarged with hypertrophy of the right ventricle and there was a patent foramen in the interventricular septum. In addition, marked arteriosclerotic changes along with dilatation and tortuosity were present in the pulmonary artery. Bilateral thrombi were seen in the vessels at a point just proximal to the level of the first division of the right and left pulmonary arterial branches. The thrombi were large, markedly adherent and definitely laminated, causing the lumen of the vessels to be considerably reduced in size. Early organization was noted in and about the point of attachment of the thrombi to the arteriosclerotic vessels.

This case is an example of one of the more frequent possibilities by which pulmonary thrombosis develops. The patient gave a history and the physical findings of congenital heart disease which at autopsy was found to be a patent interventricular septum. As a result of the increased blood volume, created by the patent septum, the right ventricle was hypertrophied and the pulmonary artery was dilated. Moreover, the increased volume increased the pulmonary artery pressure, which ultimately resulted in arteriosclerosis and subsequent bilateral thrombosis of the pulmonary vascular system.

The arteriosclerotic process involved the main stem of the artery and its right and left pulmonary branches, but it was not present below the level at which the right and left branches begin to divide into the various lobar vessels. The thrombi were attached

to the vessel walls over the arteriosclerotic plaques just proximal to the point at which the vessel divides into lobar branches. This is the usual site of formation and attachment, but in most cases the thrombus then builds in a retrograde fashion toward the heart. In this particular case the thrombi extended distally into the lobar branches, but they were not attached within these vessels. Because the main vessels were the points of origin, their lumina were materially blocked and thus the entire lung fields on both sides suffered a marked reduction in blood supply, producing the characteristic clinical syndrome.

This is an example of the type of case that Harvey and Hogg[3] had in mind when they stated that one must suspect the possibility of pulmonary artery thrombosis when a patient who has congenital heart disease suddenly develops a marked increase in the severity of his symptoms.

SUMMARY

1) A resumé of the medical literature pertaining to the subject of thrombosis of the pulmonary artery and its right and left branches has been presented.

2) Pathologic changes associated with the condition have been discussed.

3) A definite clinical syndrome produced by such a thrombus has been described.

4) A typical case report, illustrating the syndrome, and substantiated by pathological material, was made.

RESUMEN

1) Se ha presentado un resumen de la literatura médica tocante al tema de la trombosis de la arteria pulmonar y sus ramas derecha e izquierda.

2) Se han discutido las alteraciones patológicas asociadas a esta condición.

3) Se ha descrito el síndrome clínico bien definido que produce ese trombo.

4) Se presenta un informe sobre un caso típico que ilustra el síndrome y que fue verificado con tejidos patológicos.

REFERENCES

1 Kampmeier, R. H.: "Thrombosis of Main Branches of the Pulmonary Artery," *J. Thoracic Surg.*, 3:513, 1934.
2 Dickinson, L.: "Thrombosis of the Pulmonary Artery in a Case of Congenital Stenosis of the Orifice," *Tr. Path. Soc. London,* 48:57, 1896-1897.
3 Harvey, E. B. and Hogg, P.: "Thrombosis of the Pulmonary Artery in Children," *Am. J. Dis. Child.*, 71:67, 1946.
4 Middleton, W. S.: "Abdominal Pain in Pulmonary Thrombosis," *Ann. Int. Med.*, 18:345, 1943.

5 Mallory, T. B.: "Case Records of the Massachusetts General Hospital," *New England J. Med.*, 215:982, 1936.
6 Pou, J. F. and Charr, R.: "Thrombosis of Pulmonary Artery," *Am. Rev. Tuberc.*, 37:394, 1938.
7 Covey, G. W.: "Chronic Cor Pulmonale with Report of a Case," *Ann. Int. Med.*, 18:851, 1943.
8 Barsoum, H.: "Thrombosis of Pulmonary Artery," *Brit. Med. J.*, 2:620, 1938.
9 Wade, J. L.: "Advanced Pneumoconiosis with Pulmonary Artery Thrombosis," *West Virginia Med. J.*, 36:69, 1940.
10 Gunter, J. U.: "Thrombosis of the Pulmonary Artery in Identical Twins," *Arch. Path.*, 31:211, 1941.
11 Behrentes, E. G.: "Obturator Thrombosis of the Right Pulmonary Artery and Necrosis of the Entire Lung with Hilar Bronchogenic Carcinoma," *Arch. Path.*, 33:259, 1942.
12 Balboni, V. G.: "Multiple Pulmonary Thrombi Associated with Cyanosis and Right-Sided Cardiac Hypertrophy," *New England J. Med.*, 223:896, 1940.
13 Mallory, T. B.: "Case Records of the Massachusetts General Hospital," *New England J. Med.*, 222:457, 1940.
14 Brenner, O.: "Pathology of the Vessels of the Pulmonary Circulation," *Arch. Int. Med.*, 56:1189, 1935.
15 Means, J. H. and Mallory, T. B.: "Total Occlusion of the Right Branch of the Pulmonary Artery by an Organized Thrombus," *Ann. Int. Med.*, 5:417, 1931.
16 Boswell, C. H. and Palmer, H. D.: "Progressive Thrombosis of the Pulmonary Artery," *Arch. Int. Med.*, 47:799, 1931.
17 Horine, C. F. and Warner, C. G.: "Experimental Occlusion of the Pulmonary Artery," *Arch. Surg.*, 28:139, 1934.
18 Savacool, W. J. and Charr, R.: "Thrombosis of the Pulmonary Artery," *Am. Rev. Tuberc.*, 44:42, 1941.
19 Moschowitz, Eli: "Vascular Sclerosis," *Oxford University Press*, New York, 1942.
20 Gibbon, G. H. Jr., Hopkinson, Mary and Churchill, E. D.: "Changes in the Circulation Produced by Gradual Occlusion of the Pulmonary Artery," *J. Clin. Investigation*, 11:543, 1932.
21 McGinn, S. and White, P.: "Acute Cor Pulmonale Resulting from Pulmonary Embolism," *J.A.M.A.*, 104:1473, 1935.

MOTION PICTURE SESSION AT ANNUAL MEETING

A new feature to be presented at the 15th Annual Meeting of the College will be a motion picture session to be held at the Ambassador Hotel, Atlantic City, on Friday evening, June 3. Interesting films dealing with problems of diseases of the chest will be shown. Applications should include the title of the film, author, approximate running time, whether silent or sound, color or black and white, and the size of the film. A brief resumé of the material presented in the film should accompany the application.

One evening has been set aside for the motion picture session and therefore only a limited number of films can be shown. Applications for consideration in the program should be submitted at once to Dr. Paul H. Holinger, Chairman, Committee on Scientific Program, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

CORRECTION IN THE JANUARY ISSUE

David Salkin, M.D., F.C.C.P., of the Veterans Administration Hospital, San Fernando, California, completed work on his paper, "Postmortem Pneumothorax," at the Hopemount Sanatorium and the University of West Virginia Medical School, Morgantown, West Virginia.

College Chapter News

FLORIDA CHAPTER

The Florida Chapter of the College will hold its first meeting at the Belleview Biltmore Hotel, Belleair, Florida, on April 10, in conjunction with the annual meeting of the Florida Medical Association, April 10-13. The meeting will open at 9:00 a. m. with an administrative session and election of officers. The following scientific program will be presented:

"Flight Medicine: Practical Experiences in Transportation of Ill Patients in Commercial Aviation,"
Howard K. Edwards, M.D., F.C.C.P.

"The Role of X-Ray in Pulmonary Diseases" (Slide Demonstration),
Maurice Kovnat, M.D., F.C.C.P.

"Indications for Bronchoscopy; Chronic Asthmatic and Static Asthmatic,"
Nathaniel Levin, M.D., F.C.C.P.

"Treatment of Lung Abscess,"
DeWitt C. Daughtry, M.D.

General Discussion.

"X-Ray Symposium of Common Conditions Found in the Chest,"
Physicians are requested to bring films on any problems in which they are interested. Unlimited discussion.
M. Jay Flipse, M.D., F.C.C.P., Moderator.

The present officers of the Florida Chapter are: Dr. E. C. Brunner, President, and Dr. Howard K. Edwards, Secretary-Treasuer. The Program Committee is comprised of Dr. Nathaniel Levin, Chairman, Dr. Arnold S. Anderson, and Dr. Alexander Libow.

ILLINOIS CHAPTER

The Illinois Chapter of the College held a dinner meeting and presented a scientific program at the Congress Hotel, Chicago on February 11th. The program presented was as follows:

"Photoelectric Plethysmograph and Direct Blood Pressure Measurement as an Aid in the Diagnosis of Coarctation of the Aorta,"
Melvin Goldman, M.D., St. Louis, Missouri.

"A Clinical and Pathological Correlation of Tumors of the Lung,"
Lauren V. Ackerman, M.D., St. Louis, Missouri.

"Arterial Venous Aneurysm of the Lung,"
Alfred Goldman, M.D., F.C.C.P., St. Louis, Missouri.

POTOMAC CHAPTER

The Annual Meeting of the Potomac Chapter of the College will be held at the Sheraton Belvedere Hotel, Baltimore, Maryland, on April 27, in conjunction with the Annual Meeting of the Medical and Chirurgical Faculty of the State of Maryland, April 26-27. The chapter will present their scientific program on April 27 as a section of the Medical and Chirurgical Faculty of the State of Maryland. The program will be as follows:

Title: Neoplasms of the Chest.

Moderator: W. LeRoy Dunn, M.D., F.C.C.P., Washington, D. C.

Subjects: "Tumors of the Mediastinum,"
Edward M. Kent, M.D., F.C.C.P., Pittsburgh, Pennsylvania.
"Intra Pulmonary Neoplasms,"
Edgar W. Davis, M.D., F.C.C.P., Washington, D. C.
"Tumors of the Thoracic Cage,"
John W. Strieder, M.D., Boston, Massachusetts.

Following this scientific program, the Potomac Chapter will have a business meeting and a cocktail party and banquet. An X-ray Conference will be held immediately following the banquet. Dr. Otto C. Brantigan, Baltimore, President of the Potomac Chapter, will preside at the banquet.

TEXAS CHAPTER

The Annual Meeting of the Texas Chapter of the College will be held at the Gunter Hotel, San Antonio, on May 2nd. The following program will be presented:

"Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis,"
Robert G. McCorkle, M.D., F.C.C.P., San Antonio.
Discussant: Rodger J. B. Hibbard, M.D., Legion.

"Experimental Massive Pulmonary Collapse,"
W. W. Coulter, Jr., M.D., F.C.C.P., McAllen.
Discussant: James E. Dailey, M.D., F.C.C.P., Houston.

"Important Aspects of the Relationship of Dust to Health,"
M. J. Cuen, M.D., Galveston.
Discussants: Charles M. Hendricks, M.D., F.C.C.P., El Paso;
John S. Chapman, M.D., F.C.C.P., Dallas;
John A. Wiggins, M.D., F.C.C.P., Ft. Worth.

"The Early Detection of Primary Bronchogenic Carcinoma,"
Robert R. Shaw, M.D., Dallas.
Discussants: Howard T. Barkley, M.D., Houston;
Samuel H. Haigler, M.D., Wharton.

"Carcinoma of the Lung in Children and Young Adults,"
John Roberts Phillips, M.D., F.C.C.P., Houston.
Discussant: Donald L. Paulson, M.D., Dallas.

"Anesthesia in Chest Surgery,"
Raymond F. Corpe, M.D., Sanatorium.
Discussants: Robert R. Shaw, M.D., Dallas;
George W. Waldron, M.D., F.C.C.P., Houston.

Dr. Paul A. Turner, Louisville, Kentucky, Chairman of the Board of Regents of the American College of Chest Physicians, will be guest speaker at the annual banquet. His subject will be "Modern Trends in Treatment of Pulmonary Tuberculosis." Dr. Turner will be introduced by Dr. Elliott Mendenhall, Dallas, President of the Texas Chapter of the College.

The Wisconsin Chapter of the College held a meeting at the Medford Hotel, Milwaukee on December 3rd. Dr. Douglas Gutheil presented a study of "Twenty-Five Women Ill with Tuberculosis who had been Treated with Streptomycin."

ANNUAL MEETING AMERICAN BRONCHOESOPHAGOLOGICAL ASSN.

The 30th Annual Meeting of the American Bronchoesophagological Association will be held at the Drake Hotel, Chicago, Illinois, April 18-19, 1949.

MEDICAL SERVICE BUREAU

POSITIONS AVAILABLE

Position open as assistant on sanatorium staff. Will require good knowledge of collapse therapy and x-ray interpretation. Person would also have to have duties in tuberculosis diagnostic clinic and in microfilm reading. Please state all particulars concerning self together with qualifications. Also state salary expected in addition to full maintenance. Please address Box 191A, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

Two residencies in tuberculosis available at sanatorium in California. Accredited and approved. All types of treatment for pulmonary tuberculosis including major chest surgery. Salary depending on experience and personality. Good quarters on grounds for both single and married persons. Residents must secure California license and must be U. S. citizens. Please address Box 193A, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

Resident physician wanted for fully approved and accredited sanatorium in Indiana. Full diagnostic, social and therapeutic services and active out-patient department. Salary $300 to $400 monthly with complete maintenance. Candidates must be eligible for an Indiana license. Please address Box 194A, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

Tuberculosis Staff Physicians. Approved, modern hospital, 300 beds. Metropolitan area. All departments and modern facilities for diagnosis and treatment. University affiliation. Man or woman. Good salary and complete family maintenance in new home. American citizenship, graduate of approved American school, approved state licensure required. Available before March 15; can employ at once. An active service; excellent opportunity for an industrious physician. Please address Box 195A, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

Resident physician in tuberculosis sanatorium. Training in all forms of collapse therapy. Salary $4,200 and complete maintenance for self and family. Yearly salary increase and possibility to work up. One year credit for boards in internal medicine granted. Located in resort country. University near for postgraduate training. Please address Box 196A, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

Resident physician wanted for 80-bed county sanatorium. Active out-patient department. One-year internship required. Salary up to $3,000 and maintenance. Approved by A.M.A. and College of Surgeons. Macon County Tuberculosis Sanatorium, Decatur, Illinois.

Positions open for physicians in large tuberculosis hospital. Salaries from $4,800 to $7,320 annually. Contact Personnel Office, Battey State Hospital, Rome, Ga.

Position available for Assistant Medical Superintendent Tuberculosis Sanatorium. To assist in administration of 100-bed tuberculosis sanatorium and outpatient chest clinic. Some previous experience in a tuberculosis institution required. Candidates must have a license or procure a license to practice in California before appointment. Salary range: $549 to $686. Apply: Civil Service Commission, Court House, Redwood City, California.

POSITIONS WANTED

Chest physician in Australia desires postgraduate training or permanent residence in sanatorium in the U.S.A. Experienced in the management of chest diseases, especially tuberculosis, pneumothorax, pneumolysis, bronchoscopy and minor thoracic surgery. Graduate of University of Sydney. Please address Box 240A, American College of Chest Physicians, 500 N. Dearborn St., Chicago 10, Ill.

Experienced chest physician, Fellow American College of Chest Physicians, desires position as assistant medical director of small sanatorium or hospital. Please address Box 241A, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.